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STOPPING THE SPREAD OF MONKEYPOX: EXAMINING THE FEDERAL RESPONSE

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Introduction

Chair Murray, Ranking Member Burr, distinguished members of the Committee, thank you for this opportunity to testify before you today to describe the Food and Drug Administration's (FDA's or the Agency's) monkeypox disease 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, approval, and availability of critical, safe, and effective medical products to address the monkeypox virus public health emergency.

We are closely monitoring the situation and responding aggressively, while also preparing for potential changes and shifts as the public health emergency continues. The Agency is using lessons learned from the coronavirus disease 2019 (COVID-19) response effort to inform our decision making going forward and aid in our response to monkeypox disease. For eligible Americans, getting vaccinated and following Centers for Disease Control and Prevention (CDC) guidance remain the best way to protect themselves and their families.

Presently, JYNNEOS is the only FDA-licensed vaccine in the United States that is approved for the prevention of monkeypox disease. JYNNEOS, the Modified Vaccinia Ankara (MVA) vaccine, is approved for the prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection. JYNNEOS was approved in 2019. The recent Emergency Use Authorization (EUA) allowing for intradermal administration of JYNNEOS for individuals 18 years of age and older determined to be at high risk of monkeypox infection will increase the supply of available doses by up to five-fold.

In addition, the CDC has an FDA-cleared test that can detect non-variola orthopoxviruses, including monkeypox. FDA also recently granted the first EUA for a monkeypox test, and we have issued policy guidance to support development of additional validated monkeypox tests and expand access to tests.[1]

While there is no FDA-approved treatment for monkeypox, through the use of existing FDA authorities, tecovirimat (TPOXX), an antiviral medication, is available to patients under an Expanded Access Investigational New Drug protocol (EA-IND).

Since the first positive case of monkeypox disease in the United States, FDA has taken an active role in responding to the ongoing public health threat posed by the spread of monkeypox. This testimony is only a snapshot of the continued work the Agency is doing to address the monkeypox outbreak.

[1] U.S. Food and Drug Administration, "Monkeypox Update: FDA Takes Significant Action to Help Expand Access to Testing," September 7, 2022, available at https://www.fda.gov/news-events/press-announcements/monkeypox-update-fda-takes-significant-action-help-expand-access-testing.

Supporting Timely Access to Monkeypox Vaccines

FDA's Center for Biologics Evaluation and Research (CBER) continues to use every tool available to help facilitate the development of biological products to aid in the Agency's larger effort to respond to the monkeypox public health emergency.

JYNNEOS is the only vaccine that is FDA-approved for the prevention of monkeypox disease. JYNNEOS is a live virus vaccine that contains MVA-Bavarian Nordic, a weakened, non-replicating orthopoxvirus, and was developed for use in certain populations (e.g., immunocompromised individuals) as an alternative to ACAM2000, a licensed vaccine, in the event of a smallpox bioterrorist attack. This virus strain has been safely administered to thousands of individuals intradermally in the past, both as a smallpox vaccine and in investigational studies for other zoonotic orthopoxviruses and variola viruses.[2] Further, JYNNEOS may be safely used in significantly immunocompromised individuals, including individuals with Human Immunodeficiency Virus (HIV), for whom it may not be advisable to receive certain live vaccines.

ACAM2000 is an FDA-licensed live replicating vaccinia virus vaccine approved for the prevention of smallpox disease. It is associated with a higher risk of certain serious adverse reactions compared to JYNNEOS, including myocarditis and pericarditis, which are inflammation and swelling of the heart and surrounding tissues, respectively. The risk of accidental infection by someone who just received ACAM2000 can also present serious health complications in certain populations, including those who are pregnant. The ACAM2000 vaccine also causes a blister to develop at the vaccination site. Exposure to the blister and its contents may lead to accidental infection. This risk of accidental infection following vaccination does not occur with JYNNEOS, as the vaccination does not cause a blister to form at the injection site.

In late May 2022, following reports of monkeypox in the United States, FDA worked with the Biomedical Advanced Research and Development Authority (BARDA) to expedite the submission of a manufacturing supplement to FDA to facilitate JYNNEOS production at an additional site that was originally planned for fall 2022. After receiving the supplemental application for the additional facility, FDA immediately expedited our evaluation of the application and corresponding inspection of the facility. FDA evaluated the information required to validate product quality and determined that the vaccine meets our quality standards. The evaluation and inspection were necessary to help ensure the quality and safety of the vaccine.

[2] For detailed information on the study, please visit Sharon E. Fry et al., "Comparison of lyophilized versus liquid modified vaccinia Ankara (MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naïve subjects," *Vaccine*, 33:39, September 22, 2015, pp. 5225-34, available at https://www.sciencedirect.com/science/article/pii/S0264410X15008762?via%3Dihub.

On July 26, 2022, FDA approved a supplemental biologics license application for JYNNEOS, which allowed for additional doses manufactured at a facility in Europe to be further distributed and administered in the United States to help address the monkeypox outbreak.

Given the emerging public health need, FDA facilitated advance shipments of manufactured doses to the United States for prepositioning so that they would be onshore and ready to be distributed once we completed our inspection and approved the manufacturing changes.

On August 9, 2022, FDA issued an EUA for JYNNEOS to allow healthcare providers to administer the vaccine intradermally (between the layers of the skin) for individuals 18 years of age and older determined to be at high risk for monkeypox infection. The EUA also allows for use of the vaccine in individuals younger than 18 years of age determined to be at high risk for monkeypox infection; in these individuals, JYNNEOS is administered by subcutaneous injection. For all age groups, JYNNEOS is given as a two-dose series, four weeks apart. In issuing this EUA, FDA determined that the known and potential benefits of JYNNEOS outweigh the known and potential risks for the authorized uses.

A 2015 clinical study[3] evaluated a two-dose series of JYNNEOS given intradermally compared to subcutaneously in individuals 18 years of age and older. Individuals who received the vaccine intradermally received a lower volume (one-fifth) of the vaccine than individuals who received the vaccine subcutaneously. The results of this study demonstrated that intradermal administration produced a similar immune response to subcutaneous administration. Administration by the intradermal route resulted in more redness, firmness, itchiness, and swelling at the injection site, but less pain.

The JYNNEOS EUA will increase the total number of doses available for use by up to five-fold.

To support FDA's authorization of two doses of JYNNEOS administered by the subcutaneous route of administration in individuals younger than 18 years of age, FDA considered the available JYNNEOS safety and immune response data in adults as well as the historical data with use of live vaccinia virus smallpox vaccine in pediatric populations.

Following the EUA, the Agency has participated in calls with healthcare providers to discuss the newly authorized administration method and provide the most up-to-date information to those administering the vaccine.[4] It is important to recognize that we do not have clinical data on safety and efficacy of JYNNEOS, so FDA will continue to monitor the safety data received from

[3] Ibid.

[4] The most up-to-date information can be found on FDA's monkeypox homepage: U.S. Food and Drug Administration, "FDA Monkeypox Response," updated continuously, available at https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/fda-monkeypox-response.

jurisdictions as administration of JYNNEOS increases across the United States. Additionally, NIH has initiated a prospective clinical trial to obtain these data.

Supporting Monkeypox Test Development and Timely Test Access

Since the first case of monkeypox was detected in the United States, FDA's Center for Devices and Radiological Health (CDRH) has been working closely with CDC, laboratories, and commercial manufacturers to support test development and help make monkeypox tests more readily available to consumers who need them. CDC has an FDA-cleared test that can detect non-variola orthopoxviruses, including monkeypox, by a swab from a lesion (rash or growth). The Agency engaged early with CDC and other agencies to support 67 CDC Laboratory Response Network laboratories' use of the FDA-cleared test. FDA and federal authorities subsequently worked with industry to help make this test available through five large commercial laboratories (LabCorp, Mayo, Aegis, Sonic, and Quest). Presently, more testing capacity for monkeypox exists than is being used.[5] However, FDA knows the value of assuring patients have test options and timely access to test results – and we have continued working toward expansion of testing capacity nationwide in an effort to stem the spread of the virus.

FDA has been working proactively with commercial manufacturers on the development and validation of both laboratory-based molecular diagnostic tests and rapid molecular or antigen tests for use at the point-of-care (such as clinics) or at home.

As part of this close work with CDC and the private sector, FDA has undertaken additional efforts that are critical to support test developers, laboratories, and patients as the nation responds to the monkeypox virus outbreak. To increase the availability, accessibility, and throughput of the CDC test, FDA has updated the test's clearance and provided temporary enforcement discretion as needed regarding the test's use with additional instruments, extraction reagents, and automated extractions. FDA has also been monitoring the availability of test components and testing supplies and provided temporary enforcement discretion regarding the use of substitute components to help address shortage issues. Subsequently, these laboratories have had additional options and flexibility, which helps to improve timely patient access to monkeypox tests throughout the country. FDA also has provided temporary enforcement discretion regarding laboratories' reporting of test results from the CDC test, allowing results reported as "detected," and "positive," rather than "presumed positive," so that samples do not need to be sent to CDC for confirmation prior to initiating treatment.

In addition, FDA has reached out to commercial control manufacturers to encourage them to produce orthopoxvirus and monkeypox control material that can be used for test development and test validation as well as batch testing once clinical testing has been launched. Control

[5] For the latest data on testing capacity and positivity rates please visit CDC's website: Centers for Disease Control and Prevention, "Monkeypox Signs and Symptoms," available at https://www.cdc.gov/poxvirus/monkeypox/index.html.

material is now available from at least two sources – the National Institute of Standards and Technology and a commercial provider. This control material is another important resource for laboratories that are working to develop additional tests for monkeypox.

On September 8, 2022, Secretary Xavier Becerra signed a declaration under section 564 of the Federal Food, Drug, and Cosmetic Act to allow the FDA Commissioner to issue emergency use authorizations for in vitro diagnostics to expand the availability of tests for monkeypox. On the same day, FDA issued the first EUA for a monkeypox in vitro diagnostic – the Quest Diagnostics Monkeypox Virus Qualitative Real-Time PCR[6] – intended to detect monkeypox and other non-variola orthopoxvirus DNA using lesion swab specimens.

As part of the guidance, FDA has provided voluntary templates that test developers may use when validating a test or when submitting an EUA request. These templates include recommendations – not requirements – for how a developer could validate a test to help ensure it is appropriately accurate and reliable. FDA intends to update its recommendations, as needed, in response to the developing emergency.

FDA will also continue its partnership with the National Institutes of Health's (NIH) Independent Test Assessment Program (ITAP),[7] which helped streamline validation and authorization of COVID tests. ITAP showed the great value of an independent validation program for tests and, based on this experience, we will partner with NIH/ITAP to help streamline validation and authorization of point-of-care and home monkeypox virus tests. On September 7, 2022, ITAP announced it is accepting proposals.[8]

FDA continues actively working with private and public entities on monkeypox test development and availability. This includes meeting regularly with the CDC, academic, commercial, and public health laboratories and addressing monkeypox during FDA's monthly virtual town hall series for test developers.[9] FDA is also fully engaged with CDC and key stakeholders in the laboratory community under a memorandum of understanding to collaborate on enhancing diagnostic surge testing capacity during public health emergencies.[10] This has helped facilitate

[6] U.S. Food and Drug Administration, letter (EUA) to Quest Diagnostics Incorporated, September 7, 2022, available at https://www.fda.gov/media/161454/download.
[7] U.S. Department of Health and Human Services, "New HHS Actions Add to Biden Administration Efforts to Increase Access to Easy-to-Use Over-the-Counter COVID-19 Tests," October 25, 2021, available at https://www.hhs.gov/about/news/2021/10/25/new-hhs-actions-add-biden-administration-efforts-increase-access-easy-use-over-counter-covid-19-tests.html.
[8] National Institute of Biomedical Imaging and Bioengineering, "Independent Test Assessment Program (ITAP): Announcement: See New Opportunity for Monkeypox Virus Diagnostics Below," available at https://www.nibib.nih.gov/covid-19/radx-tech-program/ITAP.
[9] U.S. Food and Drug Administration, "Virtual Town Hall Series – Coronavirus (COVID-19) Test Development and Validation," August 24, 2022, available at https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/virtual-town-hall-series-coronavirus-covid-19-test-development-and-validation-07272022.
[10] MOU 225-22-020, "Memorandum of Understanding for Diagnostic Surge Capacity for Public Health Emergencies," effective May 6, 2022, available at https://www.cdc.gov/csels/dls/documents/2022-revised-mou-for-surge-capacity_final_signed.pdf.

communications between FDA, our federal partners, and laboratory professional associations and large commercial laboratories, including, for example, helping gain an understanding of willingness to participate in developing increased testing capacity, any barriers to such participation, and suggestions on next steps.

FDA will continue working with our U.S. government partners, laboratories, and commercial manufacturers to support access to the CDC test and the development of additional tests. FDA's efforts are critical to help ensure patients can depend on their test results and receive care as needed, and to avoid or mitigate further spread of monkeypox.

Supporting Timely Access to and Careful Evaluation of Monkeypox Therapeutics

Currently there are no FDA-approved products for the treatment of monkeypox. Tecoviramat, or TPOXX, was approved for the treatment of smallpox in adults and children in 2018 under FDA's "Animal Rule" and is being made available for the treatment of monkeypox under an EA-IND through FDA's Expanded Access program.

The Animal Rule[11] allows efficacy to be established based on adequate and well-controlled animal efficacy studies when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans for the disease of interest and when conducting clinical trials in humans is not feasible or ethical. Smallpox is caused by the variola virus. Animal studies using variola virus are not consistently reproducible and do not mimic human disease. They are extremely challenging to conduct as research is restricted to two maximum-containment laboratories located in the United States and Russia. TPOXX's efficacy for the treatment of smallpox was established, and the drug approved, based on studies in animal models using orthopoxviruses related to the smallpox virus — specifically, nonhuman primates infected with monkeypox virus and rabbits infected with rabbitpox virus. Safety data was obtained in healthy human volunteers without monkeypox virus infection.

The Animal Rule can be used only when it is not feasible or ethical to conduct human clinical trials, as was the case with smallpox. Human studies of TPOXX's efficacy against smallpox disease were not ethical or feasible as smallpox has been eradicated. The Animal Rule was not a viable regulatory pathway to approve tecovirimat for the treatment of monkeypox as the disease was endemic in West and Central Africa, and it was both feasible and ethical to conduct clinical trials in humans.

It is important to note that drugs that show efficacy in animal studies are not always effective in humans. Currently there are no human data demonstrating the efficacy of TPOXX for the treatment of monkeypox or its safety and pharmacokinetic profile in patients with monkeypox; therefore we do not know if TPOXX will be beneficial in treating patients with monkeypox.

[11] For more information on the Animal Rule, please visit U.S. Food and Drug Administration, "Animal Rule Approvals," June 2, 2022, available at https://www.fda.gov/drugs/nda-and-bla-approvals/animal-rule-approvals.

Thus, conducting randomized, controlled trials to assess tecovirimat's safety and efficacy in humans is essential.

In parallel with planning for a randomized controlled trial, access to TPOXX for the treatment of monkeypox has been made available through an EA-IND held by CDC under FDA's Expanded Access program. FDA has worked closely with CDC to streamline the protocol based on input from stakeholders to reduce data collection and reporting requirements.

We understand, however, that challenges remain with the current EA-IND mechanism, and we continue to consider all potential regulatory options to best address this situation. Regardless of the regulatory mechanism used to facilitate access to TPOXX, it is important that access does not compromise the ability to conduct randomized, controlled trials that can establish whether TPOXX helps patients with monkeypox. Such clinical trials will be key to any potential consideration of approval of TPOXX.

It is also critical to note that viral resistance to tecovirimat is a concern. TPOXX works by inhibiting a protein called VP37 that all orthopoxviruses share. Even a small change to the VP37 protein can have a large impact on the antiviral activity of tecovirimat. Therefore, judicious use of TPOXX and careful monitoring for the development of viral resistance are of paramount importance for stewardship of this potentially beneficial drug while we study it in clinical trials.

Conclusion

FDA continues to advance its mission to protect and promote public health by helping to ensure the safety of human and animal food, and the safety and effectiveness of medical products. We take our public health mandate very seriously and will continue to work each day to help end the monkeypox public health emergency. FDA and our HHS partners are working tirelessly to ensure a robust and comprehensive response to monkeypox that considers the ever-changing nature of the outbreak. We continue to communicate with the American public and make regulatory decisions based on data and sound science. The Agency looks forward to working with sponsors to increase vaccine supply, increase testing options and capacity, and increasing the number of available treatments, while ensuring that the products meet applicable standards for safety and effectiveness. I hope to continue working with the Committee on these efforts. Thank you again for the opportunity to testify today.