Xavier Beccera
Secretary
Department of Health and Human Services

Rochelle Walensky, MD, MPH
Director
Centers for Disease Control and Prevention

Robert Califf, MD
Commissioner
Food and Drug Administration

CC: Anthony Fauci, MD, Director, National Institute of Allergy and Infectious Disease
Raj Panjabi, MD, Senior Director, Global Health Security and Biodefense, National Security Council

July 15, 2022

Dear Secretary Becerra, Dr. Walensky & Dr. Califf,

In our clinical and advocacy responses to the monkeypox outbreak, we have witnessed first-hand how the CDC's "non-research expanded access Investigational New Drug" (EA-IND) protocol creates significant barriers to accessing tecovirimat (TPOXX), an antiviral that can be considered for treatment in people infected with monkeypox virus. Doses of TPOXX are not currently commercially available. Rather, prescribers access doses of TPOXX through the Strategic National Stockpile (SNS). The CDC currently requires prescribers access the two million courses of TPOXX stored within the SNS exclusively though the EA-IND protocol.

The current EA-IND process requires prescribers to review an over one hundred page protocol to access to TPOXX for their patients.The protocol further requires prescribers collect extensive information on each patient treated with TPOXX and submit that to the FDA and CDC, including photographs of lesions, extensive information about the prescriber (including a *curriculum vitae*), schedule multiple follow up visits, and send optional blood samples to CDC.[1] No resources are provided by the CDC or the federal government to facilitate completion of these requirements of the EA-IND.

[1] CDC. (2022) 'Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Orthopoxvirus Infections'. Available at: https://drive.google.com/file/d/1K2jSEQ7_hTXuDiZj3dW6MniR49HQtLxX/view?usp=sharing

Furthermore, even though the EA-IND protocol alleges that it does not constitute human subject research, many institutions require institutional review board (IRB) oversight or waiver of any drug administered through an IND process. This adds to the already onerous requirement of the EA-IND process itself.

The need for an IND for TPOXX is highly unusual given that the drug was fully approved by the U.S. FDA on 13 July 2018.[2] Once a drug is approved by the FDA in the United States, prescribers have the authority to prescribe a drug for an indication that it is not formally approved for — a practice commonly known as "off label prescribing" — without formal approval from the FDA or the use of an IND.[3] It appears that in this case, the need to use the EA-IND process is simply a result of the federal government controlling access to the drug through the SNS.

Given the lack of active variola virus (the virus that causes smallpox) transmission and infection, and the inability to do human challenge trials, TPOXX was approved via the "animal rule" pursuant to 21 C.F.R. § 314, subpart I. Despite being approved under the animal rule, the U.S. FDA "concluded that TPOXX® (tecovirimat) can be safely used without restrictions on distribution or use" [emphasis ours].[4]

Despite these decisions from the FDA, the CDC states it has imposed an IND on TPOXX because it is *only* FDA approved for smallpox, and *not* approved for other orthopox viruses such as monkeypox.[5] This is illogical, given that the FDA's approval of TPOXX for smallpox is based on efficacy data on monkeypox virus in non-human primates and rabbitpox virus in rabbits.[6] No variola virus data was used in the FDA approval for TPOXX, because variola virus is not currently circulating in humans and animal models do not consistently mimic what is known about human smallpox disease.[6,7]

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[2] *See* FDA. (2018) New Drug Application (NDA) Approval Letter for NDA 208627. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/208627Orig1s000ltr.PDF

[3] *See, e.g.,* Stafford S. (2008) "Regulating Off-Label Drug Use — Rethinking the Role of the FDA". *N Engl J Med*; 358:1427-1429. Available at: https://www.nejm.org/doi/full/10.1056/nejmp0802107

[4] *See* FDA. (2018) New Drug Application (NDA) Approval Letter for NDA 208627 at Page 3. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/208627Orig1s000ltr.PDF.

[5] CDC. (2022) 'Guidance for Tecovirimat Use Under Expanded Access Investigational New Drug Protocol during 2022 U.S. Monkeypox Cases', CDC.gov. Available at: https://www.cdc.gov/poxvirus/monkeypox/clinicians/Tecovirimat.html

[6] *See* Center for Drug Evaluation and Research. (2018) Clinical review for NDA 208627, pp. 11-12. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208627Orig1s000MedR.pdf

[7] Merchlinsky, M. *et al.* (2019) 'The development and approval of tecoviromat (TPOXX®), the first antiviral against smallpox', *Antiviral Research*, 168, pp. 168–174. Available at: https://doi.org/10.1016/j.antiviral.2019.06.005.

Given this, the European Medicines Agency (EMA) has already approved TPOXX for treatment in people infected with monkeypox virus, as well as smallpox and cowpox.[8] To ensure that the EA-IND processes ceases to be a barrier to clinicians and patients seeking TPOXX, we advocate two solutions:

1. The CDC rescinds its IND requirement to release TPOXX from the national stockpile

OR

2. The FDA recognizes their TPOXX approval is based on monkeypox data and authorizes TPOXX for monkeypox through the Emergency Use Authorization (EUA) process, thereby allowing the CDC to rescind its IND requirement to release TPOXX from the national stockpile

Given the lack of human data on the efficacy of TPOXX for treatment of monkeypox or other orthopoxviruses, we recognize the need to rapidly collect data on this. However, this should be done in the context of a formal clinical trial. We note that two clinical trials, both sponsored by the U.S. Army Medical Research and Development Command, aim to collect data on the safety and efficacy of TPOXX treatment (both through intravenous and oral routes of administration) for patients with monkeypox or other orthopoxvirus exposure. Both trials are actively recruiting participants; however, these trials are only open to U.S. Department of Defense (U.S. DOD) employees.[9,10] The Biden-Harris Administration should consider opening those trials to non-U.S. DOD employees or set up other clinical trials to collect data on the efficacy of TPOXX treatment.

We remain extremely concerned by the federal government's response to the monkeypox outbreak. Multiple unnecessary regulatory barriers to treatments, diagnostics, and vaccines have prevented people in the United States from accessing medical countermeasures necessary to protecting their health, allowing the continued spread of monkeypox virus. Ending the CDC's IND requirement for TPOXX is a first step to ensuring the federal government improves access to treatment for individuals infected with monkeypox virus.

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[8] *SIGA Technologies Receives Approval from the European Medicines Agency for Tecovirimat | SIGA* (2022). Available at: https://investor.siga.com/news-releases/news-release-details/siga-technologies-receives-approval-european-medicines-agency.

[9] U.S. National Clinical Trial Registry. Tecovirimat (ST-246) Treatment for Orthopox Virus Exposure. NCT Registration No: NCT02080767. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02080767

[10] U.S. National Clinical Trial Registry. Tecovirimat Intravenous Treatment for Orthopox Virus Exposure (TPOXX IV). NCT Registration No: NCT05380752. Available at:: https://www.clinicaltrials.gov/ct2/show/NCT05380752

We look forward to meeting with you at your convenience to discuss this urgent matter. Please do not hesitate to reach out with any questions, comments, or concerns.

Sincerely,

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