I. Background

FDA is announcing the availability of a revised draft guidance for industry entitled ''Assessment of Pressor Effects of Drugs.'' This draft guidance is intended to advise sponsors on the premarketing assessment of a drug's effect on blood pressure. Elevated blood pressure is known to increase the risk of stroke, heart attack, and death. The effect of a drug on blood pressure is, therefore, an important consideration in risk assessment and product labeling.

This draft guidance revises the draft guidance entitled ''Assessment of Pressor Effects of Drugs'' issued on May 31, 2018 (83 FR 25013). Based on comments received to the docket, the draft guidance was updated to include recommendations on the design of an ambulatory blood pressure monitoring study; recommendations on the types of drugs that need an ambulatory blood pressure monitoring study; modification of Figure 1 in the draft guidance to show the relationship between the increase in 10-year atherosclerotic cardiovascular disease event risk with chronic increases in systolic blood pressure; inclusion in the guidance of Table 1, which summarizes landmark clinical trials showing the reduction of major adverse cardiac events with decreases in blood pressure with antihypertensives; and considerations for product labeling. In addition, editorial changes were made to improve clarity.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on ''Assessment of Pressor Effects of Drugs.'' It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

While this draft guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3521) is not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR part 312 addressing investigational new drug applications have been approved under OMB control number 0910–0014 and the collections of information in 21 CFR part 314 addressing new drug applications have been approved under OMB control number 0910–0001.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/regulatory-information/search-fda-guidance-documents,* or *https://www.regulations.gov.*

Dated: January 31, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022–02371 Filed 2–3–22; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2021–N–0335]

Authorizations of Emergency Use of Certain Drugs and Biological Products During the COVID–19 Pandemic; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the issuance of three Emergency Use Authorizations (EUAs) (the Authorizations) under the Federal Food, Drug, and Cosmetic Act (FD&C Act), for use during the COVID–19 pandemic. FDA has issued one Authorization for a biological product as requested by AstraZeneca Pharmaceuticals LP (AZ), one Authorization for a drug product as requested by Pfizer, Inc. (Pfizer), and one Authorization for a drug product as requested by Merck Sharp & Dohme Corp. (Merck). The Authorizations contain, among other things, conditions on the emergency use of the authorized products. The Authorizations follow the February 4, 2020, determination by the Secretary of Health and Human Services (HHS) 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 a novel (new) coronavirus. The virus, now named SARS–CoV–2, causes the illness COVID–19. On the basis of such determination, the Secretary of HHS declared on March 27, 2020, that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID–19 pandemic, pursuant to the FD&C Act, subject to the terms of any authorization issued under that section. The Authorizations, which include an explanation of the reasons for issuance, are reprinted in this document.

DATES: The Authorization for AZ is effective as of December 8, 2021, the Authorization for Pfizer is effective as of December 22, 2021, and the Authorization for Merck is effective as of December 23, 2021.

ADDRESSES: Submit written requests for single copies of the EUAs to the Office of Counterterrorism and Emerging Threats, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, Rm. 4338, Silver Spring, MD 20993–0002. Send one self-addressed adhesive label to assist that office in processing your request or include a fax number to which the Authorizations may be sent. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the Authorizations.

FOR FURTHER INFORMATION CONTACT: Michael Mair, Office of Counterterrorism and Emerging Threats, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, Rm. 4340, Silver Spring, MD 20993–0002, 301–796–8510 (this is not a toll free number).

SUPPLEMENTARY INFORMATION:

I. Background

Section 564 of the FD&C Act (21 U.S.C. 360bbb–3) allows FDA to strengthen public health protections against biological, chemical, nuclear, and radiological agents. Among other things, section 564 of the FD&C Act allows FDA to authorize the use of an unapproved medical product or an unapproved use of an approved medical product in certain situations. With this EUA authority, FDA can help ensure that medical countermeasures may be used in emergencies to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by biological, chemical, nuclear, or radiological agents when there are no adequate, approved, and available alternatives (among other criteria).

II. Criteria for EUA Authorization

Section 564(b)(1) of the FD&C Act provides that, before an EUA may be issued, the Secretary of HHS must declare that circumstances exist justifying the authorization based on one of the following grounds: (1) A determination by the Secretary of Homeland Security that there is a domestic emergency, or a significant potential for a domestic emergency, involving a heightened risk of attack with a biological, chemical, radiological, or nuclear agent or agents; (2) a

determination by the Secretary of Defense that there is a military emergency, or a significant potential for a military emergency, involving a heightened risk to U.S. military forces, including personnel operating under the authority of title 10 or title 50, U.S. Code, of attack with (A) a biological, chemical, radiological, or nuclear agent or agents; or (B) an agent or agents that may cause, or are otherwise associated with, an imminently life-threatening and specific risk to U.S. military forces; [1] (3) a determination by the Secretary of HHS that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of U.S. citizens living abroad, and that involves a biological, chemical, radiological, or nuclear agent or agents, or a disease or condition that may be attributable to such agent or agents; or (4) the identification of a material threat by the Secretary of Homeland Security pursuant to section 319F–2 of the Public Health Service (PHS) Act (42 U.S.C. 247d–6b) sufficient to affect national security or the health and security of U.S. citizens living abroad.

Once the Secretary of HHS has declared that circumstances exist justifying an authorization under section 564 of the FD&C Act, FDA may authorize the emergency use of a drug, device, or biological product if the Agency concludes that the statutory criteria are satisfied. Under section 564(h)(1) of the FD&C Act, FDA is required to publish in the **Federal Register** a notice of each authorization, and each termination or revocation of an authorization, and an explanation of the reasons for the action. Under section 564(h)(1) of the FD&C Act, revisions to an authorization shall be made available on the internet website of FDA. Section 564 of the FD&C Act permits FDA to authorize the introduction into interstate commerce of a drug, device, or biological product intended for use in an actual or potential emergency when the Secretary of HHS has declared that circumstances exist justifying the authorization of emergency use. Products appropriate for emergency use may include products and uses that are not approved, cleared, or licensed under sections 505, 510(k), 512, or 515 of the FD&C Act (21 U.S.C. 355, 360(k), 360b, and 360e) or section 351 of the PHS Act (42 U.S.C. 262), or conditionally approved under section 571 of the FD&C Act (21 U.S.C. 360ccc). FDA may issue an EUA only if, after consultation with the HHS Assistant Secretary for Preparedness and Response, the Director of the National Institutes of Health, and the Director of the Centers for Disease Control and Prevention (to the extent feasible and appropriate given the applicable circumstances), FDA [2] concludes: (1) That an agent referred to in a declaration of emergency or threat can cause a serious or life-threatening disease or condition; (2) that, based on the totality of scientific evidence available to FDA, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that: (A) The product may be effective in diagnosing, treating, or preventing (i) such disease or condition; or (ii) a serious or life-threatening disease or condition caused by a product authorized under section 564, approved or cleared under the FD&C Act, or licensed under section 351 of the PHS Act, for diagnosing, treating, or preventing such a disease or condition caused by such an agent; and (B) the known and potential benefits of the product, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product, taking into consideration the material threat posed by the agent or agents identified in a declaration under section 564(b)(1)(D) of the FD&C Act, if applicable; (3) that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition; (4) in the case of a determination described in section 564(b)(1)(B)(ii) of the FD&C Act, that the request for emergency use is made by the Secretary of Defense; and (5) that such other criteria as may be prescribed by regulation are satisfied.

No other criteria for issuance have been prescribed by regulation under section 564(c)(4) of the FD&C Act.

III. The Authorizations

The Authorizations follow the February 4, 2020, determination by the Secretary of HHS 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 a novel (new) coronavirus. The virus, now named SARS–CoV–2, causes the illness COVID–19. Notice of the Secretary's determination was provided in the **Federal Register** on February 7, 2020 (85 FR 7316). On the basis of such determination, the Secretary of HHS declared on March 27, 2020, that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID–19 pandemic, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section. Notice of the Secretary's declaration was provided in the **Federal Register** on April 1, 2020 (85 FR 18250). Having concluded that the criteria for issuance of the Authorizations under section 564(c) of the FD&C Act are met, FDA has issued three authorizations for the emergency use of drugs and biological products during the COVID–19 pandemic. On December 8, 2021, FDA issued an EUA to AZ for the biological product EVUSHELD (tixagevimab co-packaged with cilgavimab), subject to the terms of the Authorization. On December 22, 2021, FDA issued an EUA to Pfizer for the drug PAXLOVID (nirmatrelvir co-packaged with ritonavir), subject to the terms of the Authorization. On December 23, 2021, FDA issued an EUA to Merck for the drug molnupiravir, subject to the terms of the Authorization. The initial Authorizations, which are included below in their entirety after section IV of this document (not including the authorized versions of the fact sheets and other written materials), provide an explanation of the reasons for issuance, as required by section 564(h)(1) of the FD&C Act. Any subsequent reissuances of these Authorizations can be found on FDA's web page at: *https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.*

IV. Electronic Access

An electronic version of this document and the full text of the Authorizations and are available on the internet at: *https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.*

BILLING CODE 4164–01–P

[1] In the case of a determination by the Secretary of Defense, the Secretary of HHS shall determine within 45 calendar days of such determination, whether to make a declaration under section 564(b)(1) of the FD&C Act, and, if appropriate, shall promptly make such a declaration.

[2] The Secretary of HHS has delegated the authority to issue an EUA under section 564 of the FD&C Act to the Commissioner of Food and Drugs.

December 8, 2021

AstraZeneca Pharmaceuticals LP
Attention: Stacey Cromer Berman, PhD
Senior Regulatory Affairs Director and Team Lead
One MedImmune Way
Gaithersburg, MD 20878

RE: Emergency Use Authorization 104

Dear Dr. Cromer Berman:

This letter is in response to AstraZeneca Pharmaceuticals LP's (AstraZeneca) request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of EVUSHELD™ (tixagevimab co-packaged with cilgavimab) for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg), as described in the Scope of Authorization (Section II) of this letter, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (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 citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

Tixagevimab and cilgavimab, the active components of EVUSHELD, are neutralizing IgG1 monoclonal antibodies that bind to distinct, non-overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2. EVUSHELD is an investigational drug and is not approved for any uses, including use as pre-exposure prophylaxis of COVID-19.

Based on the review of the data from the PROVENT clinical trial (NCT04625725), a Phase III randomized, double-blind, placebo-controlled clinical trial, it is reasonable to believe that EVUSHELD may be effective for use as pre-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg), as described

[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*. February 4, 2020.
[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of EVUSHELD outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of EVUSHELD for use as pre-exposure prophylaxis of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of EVUSHELD for pre-exposure prophylaxis of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that EVUSHELD may be effective for use as pre-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg), as described in the Scope of Authorization (section II), and that, when used under the conditions described in this authorization, the known and potential benefits of EVUSHELD outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of EVUSHELD as pre-exposure prophylaxis of COVID-19 as further described in the Scope of Authorization (section II).[3]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized EVUSHELD will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. AstraZeneca will supply EVUSHELD to authorized distributor(s)[4], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

- EVUSHELD may only be used in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

[3] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[4] "Authorized Distributor(s)" are identified by AstraZeneca as an entity or entities allowed to distribute authorized EVUSHELD.

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination[5] **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

Limitations on Authorized Use

- Evusheld is **not** authorized for the following uses in individuals:
  - For treatment of COVID-19, or
  - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- For individuals who have received a COVID-19 vaccine, EVUSHELD should be administered at least two weeks after vaccination.
- The use of EVUSHELD covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

EVUSHELD is supplied as a single carton (NDC 0310-7442-02) containing 1 single-dose vial of tixagevimab injection and 1 single-dose vial of cilgavimab injection.

Tixagevimab injection (NDC 0310-8895-01) is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution supplied in a single-dose vial for intramuscular use. The vial stoppers are not made with natural rubber latex. Each 1.5 mL contains 150 mg tixagevimab, L- histidine (2.4 mg), L- histidine hydrochloride monohydrate (3.0 mg), polysorbate 80 (0.6 mg), sucrose (123.2 mg), and Water for Injection, USP.

[5] For additional information please see https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Healthcare providers should consider the benefit-risk for an individual patient.

Cilgavimab injection (NDC 0310-1061-01) is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution supplied in a single-dose vial for intramuscular use. The vial stoppers are not made with natural rubber latex. Each 1.5 mL contains 150 mg cilgavimab, L-histidine (2.4 mg), L- histidine hydrochloride monohydrate (3.0 mg), polysorbate 80 (0.6 mg), sucrose (123.2 mg), and Water for Injection, USP.

Unopened vials of tixagevimab and cilgavimab must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Vials must not be frozen or shaken. Unused portions must be discarded.

EVUSHELD is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients, parents, and caregivers, respectively, through AstraZeneca's website www.EVUSHELD.com (referred to as the "authorized labeling"):

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for EVUSHELD
- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of EVUSHELD for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of EVUSHELD, when used for pre-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg) and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that EVUSHELD may be effective for pre-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg) when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that EVUSHELD (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), EVUSHELD is authorized for use as pre-exposure prophylaxis of COVID-19 as described in this Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

AstraZeneca and Authorized Distributors[6]

A. AstraZeneca and authorized distributor(s) will ensure that EVUSHELD is distributed with the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers as described in Section II of this Letter of Authorization.

B. AstraZeneca and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. AstraZeneca and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving EVUSHELD. AstraZeneca will provide to all relevant stakeholders a copy of this Letter of Authorization and communicate any subsequent amendments that might be made to this Letter of Authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. AstraZeneca may request changes to this authorization, including to the authorized Fact Sheets for EVUSHELD. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[7]

E. AstraZeneca may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of EVUSHELD as described in this Letter of Authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for EVUSHELD are prohibited. If the Agency notifies AstraZeneca that any instructional and educational materials are

[6] "Authorized Distributor(s)" are identified by AstraZeneca as an entity or entities allowed to distribute EVUSHELD for the use authorized in this letter.

[7] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

inconsistent with the authorized labeling, AstraZeneca must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require AstraZeneca to issue corrective communication(s).

F. AstraZeneca will report to FDA serious adverse events and all medication errors associated with the use of EVUSHELD for its authorized use that are reported to AstraZeneca using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

Submitted reports under both options should state: "EVUSHELD use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. AstraZeneca will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with drug product distributed under this emergency use authorization for EVUSHELD that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information should be submitted for all potentially impacted lots.

AstraZeneca will include in its notification to the Agency whether the batch, or batches, in question will be recalled.

If not included in its initial notification, AstraZeneca must submit information confirming that AstraZeneca has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. AstraZeneca must submit this

information as soon as possible but no later than 45 calendar days from the initial notification.

I. AstraZeneca will manufacture EVUSHELD to meet all quality standards and per the manufacturing process and control strategy as detailed in AstraZeneca's EUA request. AstraZeneca will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

J. Through a process of inventory control, AstraZeneca and authorized distributor(s) will maintain records regarding distribution of EVUSHELD (i.e., lot numbers, quantity, receiving site, receipt date).

K. AstraZeneca will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of AstraZeneca's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. AstraZeneca will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

L. FDA may require AstraZeneca to assess the activity of the authorized EVUSHELD against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). AstraZeneca will perform the required assessment in a manner and timeframe agreed upon by AstraZeneca and the Agency. AstraZeneca will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. AstraZeneca will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

M. AstraZeneca shall provide samples as requested of tixagevimab and of cilgavimab to the U.S. Department of Health and Human Services (HHS) for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of the individual drug substances for tixagevimab and cilgavimab may include, but are not limited to, cell culture potency assays, protein binding assays, cell culture variant assays (pseudotyped virus-like particles and/or authentic virus), and *in vivo* efficacy assays.

N. AstraZeneca must provide the following information to the Agency:

- All anti-drug antibody (ADA) assessments that have not been completed at the time of this authorization for subjects from the PROVENT clinical trial

for days 1, 29, 58, and 183 by April 22, 2022.

- Interim analysis results through Day 28 for the first 50 subjects to receive a second dose from the PROVENT repeat-dose sub-study by April 22, 2022.
- AstraZeneca must conduct an additional study attempting to select for SARS-CoV-2 with reduced susceptibility to tixagevimab in culture. Such study must employ alternative strategies as agreed upon between AstraZeneca and the Agency. AstraZeneca must provide the Agency with a proposed protocol by January 7, 2022. AstraZeneca must submit a report of summary findings as soon as available, but no later than June 30, 2022.
- Report from AstraZeneca's study evaluating the potential for tixagevimab and cilgavimab to mediate antibody-dependent enhancement of infection using sub-saturating concentrations of each monoclonal antibody by June 30, 2022.
- Final results from PROVENT and STORM CHASER by December 30, 2022. Results, to include baseline and all subsequent study visits, of the following biomarkers from the PROVENT repeat-dose sub-study: d-dimer, P-selectin, thrombin, and Factor VIII.
- Topline data, to include safety, pharmacokinetic, ADA, and biomarker results for thrombotic events from the first 9 months of the PROVENT repeat-dose sub-study by January 31, 2023.
- Monthly aggregate reports for serious adverse events in the Cardiac Disorder System Order Class (SOC) and other non-cardiac thrombotic serious adverse events.

O. AstraZeneca and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom EVUSHELD Is Distributed and Healthcare Providers Administering EVUSHELD

P. Healthcare facilities and healthcare providers will ensure that they are aware of the Letter of Authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients, parents, and caregivers, respectively, through appropriate means, prior to administration of EVUSHELD.

Q. Healthcare facilities and healthcare providers receiving EVUSHELD will track all serious medication errors and adverse events that are considered to be potentially attributable to EVUSHELD use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports should state, "EVUSHELD use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis. A copy of the completed FDA Form 3500 should also be provided to AstraZeneca per the instructions in the authorized labeling.

R. Healthcare facilities and healthcare providers will ensure that appropriate storage and cold chain is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.

S. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of EVUSHELD for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

T. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by AstraZeneca and/or FDA. Such records will be made available to AstraZeneca, HHS, and FDA for inspection upon request.

U. Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Conditions Related to Printed Matter, Advertising, and Promotion

V. All descriptive printed matter, advertising, and promotional materials relating to the use of EVUSHELD under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling" or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of EVUSHELD under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 at the time of initial dissemination or first use.

If the Agency notifies AstraZeneca that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions V-X of this EUA, AstraZeneca must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require AstraZeneca to issue corrective communication(s).

W. No descriptive printed matter, advertising, or promotional materials relating to the use of EVUSHELD under this authorization may represent or suggest that EVUSHELD is safe or effective when used as pre-exposure prophylaxis of COVID-19 as described in the Scope of Authorization (Section II).

X. All descriptive printed matter, advertising, and promotional material, relating to the use of EVUSHELD under this authorization clearly and conspicuously shall state that:

- EVUSHELD has not been approved, but has been authorized for emergency use by FDA under an EUA, for pre-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg); and

- The emergency use of EVUSHELD is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,
/s/

Jacqueline A. O'Shaughnessy, Ph.D.
Acting Chief Scientist
Food and Drug Administration

December 22, 2021

Pfizer, Inc.
Attention: Karen Baker
Director, Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

RE: Emergency Use Authorization 105

Dear Ms. Baker:

This letter is in response to Pfizer, Inc.'s (Pfizer) request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of PAXLOVID (nirmatrelvir co-packaged with ritonavir) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults and pediatric patients pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (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 citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

PAXLOVID is comprised of nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication. PAXLOVID is not approved for any use, including for use for the treatment of COVID-19.

Based on the totality of scientific evidence available to FDA, including data from the clinical trial EPIC-HR (NCT04960202), a Phase 2/3 randomized, double blind, placebo-controlled clinical trial, it is reasonable to believe that PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing

[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, February 4, 2020.
[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of PAXLOVID outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in certain adults and pediatric patients, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of PAXLOVID for the treatment of COVID-19, when administered as described in the Scope of Authorization (Section II), meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (section II), and that, when used under the conditions described in this authorization, the known and potential benefits of PAXLOVID outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.[3]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized PAXLOVID will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Pfizer will supply PAXLOVID to authorized distributor(s)[4], who will distribute to

[3] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[4] "Authorized Distributor(s)" are identified by Pfizer as an entity or entities allowed to distribute authorized PAXLOVID.

healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

- PAXLOVID may only be used by healthcare providers to treat mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk[5] for progression to severe COVID-19, including hospitalization or death;

  Limitations on Authorized Use

  - PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.[6]
  - PAXLOVID is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19.
  - PAXLOVID is not authorized for use for longer than 5 consecutive days.

- PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).[7]

- The use of PAXLOVID covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

PAXLOVID consists of two 150 mg tablets of nirmatrelvir that are co-packaged with one 100 mg tablet ritonavir.

Nirmatrelvir is supplied as an oval, pink, immediate-release, film-coated tablet debossed with "PFE" on one side and "3CL" on the other side.

Ritonavir is supplied as a white, film-coated, ovaloid tablet debossed with the "a" logo and the code NK.

The authorized storage and handling information for PAXLOVID is included in the authorized Fact Sheet for Healthcare Providers.

[5] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

[6] Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

[7] The term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See section 201(a)(1) of the Act.

PAXLOVID is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients, parents, and caregivers, respectively, through Pfizer's website www.COVID19oralRX.com (referred to as the "authorized labeling"):

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for PAXLOVID
- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of PAXLOVID for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of PAXLOVID, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that PAXLOVID may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that PAXLOVID (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of PAXLOVID under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), PAXLOVID is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Pfizer and Authorized Distributors[8]

A. Pfizer and authorized distributor(s) will ensure that PAXLOVID is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers as described in Section II of this Letter of Authorization.

[8] Supra at Note 4.

B. Pfizer and authorized distributor(s) will ensure that appropriate storage is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Pfizer and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving PAXLOVID. Pfizer will provide to all relevant stakeholders a copy of this Letter of Authorization and communicate any subsequent amendments that might be made to this Letter of Authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Pfizer may request changes to this authorization, including to the authorized Fact Sheets for PAXLOVID. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[9]

E. Pfizer may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of PAXLOVID as described in this Letter of Authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for PAXLOVID are prohibited. If the Agency notifies Pfizer that any instructional and educational materials are inconsistent with the authorized labeling, Pfizer must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Pfizer to issue corrective communication(s).

F. Pfizer will report to FDA serious adverse events and all medication errors associated with the use of PAXLOVID for its authorized use that are reported to Pfizer using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

[9] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

Submitted reports under both options must state: "PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. Pfizer will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with drug product distributed under this emergency use authorization for PAXLOVID that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Pfizer will include in its notification to the Agency whether the batch, or batches, in question will be recalled.

If not included in its initial notification, Pfizer must submit information confirming that Pfizer has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Pfizer must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Pfizer will manufacture PAXLOVID to meet all quality standards and per the manufacturing process and control strategy as detailed in Pfizer's EUA request. Pfizer will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

J. Through a process of inventory control, Pfizer and authorized distributor(s) will maintain records regarding distribution of PAXLOVID (i.e., lot numbers, quantity, receiving site, receipt date).

K. Pfizer will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2 and will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted. Updated data listings summarizing amino acid variability should be provided at least monthly for Mpro amino acid sequences, and at least every 2 months for Mpro cleavage site amino acid sequences. The data listings should include a cumulative list of amino acid polymorphisms detected in genomic database(s), highlighting changes/variants that are increasing in frequency from the previous month.

L. FDA may require Pfizer to assess the activity of the authorized PAXLOVID against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Pfizer will perform the required assessment in a manner and timeframe agreed upon by Pfizer and the Agency. Pfizer will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Pfizer will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

M. Pfizer shall provide samples as requested of the authorized nirmatrelvir to the U.S. Department of Health and Human Services (HHS) for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein(s) or target cleavage sites) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized nirmatrelvir may include, but are not limited to, cell culture potency assays, biochemical assays, and in vivo efficacy assays.

N. Pfizer must provide the following information to the Agency:

1. Pfizer must conduct cell culture phenotypic analyses of recombinant SARS-CoV-2 viruses or replicons carrying specific amino acid changes potentially associated with reduced nirmatrelvir susceptibility in nonclinical or clinical studies, or polymorphisms emerging in novel SARS-CoV-2 variants. Specific amino acid changes that should be characterized include the following:
   - amino acid changes associated with reduced nirmatrelvir susceptibility in biochemical assays,
   - natural amino acid polymorphisms in Mpro that come in contact with or in close proximity (<5 Å) to bound nirmatrelvir,
   - amino acid changes associated with nirmatrelvir/ritonavir treatment emergence, treatment failure, or prolonged virologic shedding or rebound in clinical trials, and
   - amino acid polymorphisms identified in resistance surveillance analyses.

   Amino acid changes in both Mpro and Mpro cleavage sites should be considered in these analyses. Specific amino acid changes of interest for

phenotypic characterization in cell culture assays currently include Mpro substitutions Y54A, E55L, F140A, S144A, E166A, H172Y, Q189K, and A260V. When warranted due to technical challenges, alternative approaches to the requested cell culture assays will be considered on a case-by-case basis. Pfizer must submit a preliminary summary report no later than February 28, 2022 for any currently ongoing studies, and at least every 6 months thereafter as additional data accumulate.

2. Pfizer must evaluate the cell culture antiviral activity of nirmatrelvir against an authentic SARS-CoV-2 isolate representative of the Omicron variant. Pfizer must submit a summary report no later than February 28, 2022.
3. Pfizer must conduct studies characterizing potential nirmatrelvir resistance mechanisms in SARS-CoV-2 in cell culture, including selection and genotypic and phenotypic characterization of nirmatrelvir-resistant virus. Pfizer must submit a brief monthly progress report on these studies, a preliminary summary report no later than April 30, 2022, and a final report within 30 days of study completion.
4. Pfizer must complete analyses of SARS-CoV-2 shedding and nucleotide sequencing from the EPIC-HR clinical trial. Viral sequencing analyses should be conducted for all clinical samples with sufficient viral RNA levels, including samples collected at baseline, on-treatment and post-treatment, to identify and characterize the potential emergence or persistence of amino acid changes associated with PAXLOVID treatment. Pfizer must submit a summary of available data (including analysis-ready datasets) no later than February 28, 2022, and a final report and associated datasets (including analysis-ready datasets and raw fastq NGS data) no later than April 30, 2022.
5. Pfizer will submit the clinical study report containing data from all enrolled subjects in the EPIC-HR clinical trial no later than January 15, 2022.
6. Pfizer will provide results from a safety and pharmacokinetic study evaluating PAXLOVID as treatment of mild-to-moderate COVID-19 in patients with severe renal impairment (for both patients requiring and not requiring hemodialysis), with the study protocol submitted no later than March 31, 2022.
7. Pfizer will provide the audited final report of the rat PPND study, *An Oral (Gavage) Study of the Effects of PF-07321332 on Pre- and Postnatal Development, Including Maternal Function in Rats,* no later than April 30, 2022.

O. Pfizer and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

<u>Healthcare Facilities to Whom PAXLOVID Is Distributed and Healthcare Providers Administering PAXLOVID</u>

P. Healthcare facilities and healthcare providers will ensure that they are aware of the Letter of Authorization, and the terms herein, and that the authorized Fact Sheets are made

available to healthcare providers and to patients, parents, and caregivers, respectively, through appropriate means, prior to administration of PAXLOVID.

Q. Healthcare facilities and healthcare providers receiving PAXLOVID will track all serious medication errors and adverse events that are considered to be potentially attributable to PAXLOVID use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports must state, "PAXLOVID use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis. A copy of the completed FDA Form 3500 must also be provided to Pfizer per the instructions in the authorized labeling.

R. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.

S. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of PAXLOVID for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

T. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Pfizer and/or FDA. Such records will be made available to Pfizer, HHS, and FDA for inspection upon request.

U. Healthcare facilities and providers will report therapeutics information and utilization data as directed by HHS.

Conditions Related to Printed Matter, Advertising, and Promotion

V. All descriptive printed matter, advertising, and promotional materials relating to the use of PAXLOVID under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling" or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of PAXLOVID under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).

- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 at the time of initial dissemination or first use.

If the Agency notifies Pfizer that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions V-X of this EUA, Pfizer must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Pfizer to issue corrective communication(s).

W. No descriptive printed matter, advertising, or promotional materials relating to the use of PAXLOVID under this authorization may represent or suggest that PAXLOVID is safe or effective when used for the treatment of COVID-19.

X. All descriptive printed matter, advertising, and promotional material, relating to the use of PAXLOVID under this authorization clearly and conspicuously shall state that:

- PAXLOVID has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high-risk for progression to severe COVID-19, including hospitalization or death; and

- The emergency use of PAXLOVID is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

/s/

Jacqueline A. O'Shaughnessy, Ph.D.
Acting Chief Scientist
Food and Drug Administration

December 23, 2021

Merck Sharp & Dohme Corp.
Attention: Sushma Kumar, PhD, PMP
Senior Director, Global Regulatory Affairs and Clinical Safety
1 Merck Drive
PO Box 100
Whitehouse Station, NJ 08889-0100

RE: Emergency Use Authorization 108

Dear Dr. Kumar:

This letter is in response to Merck Sharp & Dohme Corp.'s (Merck) request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of molnupiravir for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults who are at high-risk for progression to severe COVID-19, including hospitalization or death, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (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 citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis. Molnupiravir is not FDA-approved for any uses, including use as treatment for COVID-19.

Based on the review of the data from the MOVe-OUT clinical trial (NCT04575597), a Phase III randomized, double-blind, placebo-controlled clinical trial studying molnupiravir for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, it is reasonable to believe that molnupiravir may be effective for the treatment of mild-to-moderate COVID-19 in adults

[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, February 4, 2020.
[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of molnupiravir outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of molnupiravir for the treatment of mild-to-moderate COVID-19 in adults who are at high-risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of molnupiravir for treatment of mild-to-moderate COVID-19, when administered as described in the Scope of Authorization (Section II), meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that molnupiravir may be effective for the treatment of mild-to-moderate COVID-19 in adults who are at high-risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (section II), and that, when used under the conditions described in this authorization, the known and potential benefits of molnupiravir outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of molnupiravir for the treatment of mild-to-moderate COVID-19 in adults as further described in the Scope of Authorization (section II).[3]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized molnupiravir will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Merck will supply molnupiravir to authorized distributor(s)[4], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

[3] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[4] "Authorized Distributor(s)" are identified by Merck as an entity or entities allowed to distribute authorized molnupiravir.

- Molnupiravir may only be used for the treatment of mild-to-moderate COVID-19 in adults:
    - With positive results of direct SARS-CoV-2 viral testing, and
    - Who are at high-risk[5] for progression to severe COVID, including hospitalization or death, and
    - For whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

  Limitations on Authorized Use

    - Molnupiravir is not authorized for use in patients who are less than 18 years of age.
    - Molnupiravir is not authorized for initiation of treatment in patients requiring hospitalization due to COVID-19.[6] Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19.
    - Molnupiravir is not authorized for use for longer than 5 consecutive days.
    - Molnupiravir is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19.

- Molnupiravir may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state[7] law to prescribe drugs in the therapeutic class to which molnupiravir belongs (i.e., anti-infectives).

- The use of molnupiravir covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

The authorized molnupiravir is supplied as a bottle (NDC-0006-5055-06, NDC-0006-5055-07) containing a sufficient quantity of molnupiravir 200 mg capsules to complete a full treatment course (i.e., 40 capsules). Molnupiravir is manufactured as a Swedish Orange, opaque capsule containing the Merck corporate logo and "82" printed in white ink.

[5] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

[6] Patients requiring hospitalization after starting treatment with molnupiravir may complete the full 5 day treatment course per the healthcare provider's discretion.

[7] The term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See section 201(a)(1) of the Act.

The authorized storage and handling information is included in the authorized Fact Sheet for Healthcare Providers.

Molnupiravir is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients and caregivers, respectively, through Merck's website www.molnupiravir.com (referred to as the "authorized labeling"):

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for molnupiravir
- Fact Sheet for Patients and Caregivers: Emergency Use Authorization (EUA) of molnupiravir for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of molnupiravir, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that molnupiravir may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that molnupiravir (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of molnupiravir product under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), molnupiravir is authorized for the treatment of COVID-19 as described in this Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Merck and Authorized Distributors[8]

A. Merck and authorized distributor(s) will ensure that molnupiravir is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers as described in Section II of this Letter of Authorization.

[8] Supra at Note 4.

B. Merck and authorized distributor(s) will ensure that appropriate storage is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Merck and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving molnupiravir. Merck will provide to all relevant stakeholders a copy of this Letter of Authorization and communicate any subsequent amendments that might be made to this Letter of Authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Merck may request changes to this authorization, including to the authorized Fact Sheets for molnupiravir. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[9]

E. Merck may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of molnupiravir as described in this Letter of Authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for molnupiravir are prohibited. If the Agency notifies Merck that any instructional and educational materials are inconsistent with the authorized labeling, Merck must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Merck to issue corrective communication(s).

F. Merck will report to FDA serious adverse events and all medication errors associated with the use of molnupiravir for its authorized use that are reported to Merck using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

[9] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

Submitted reports under both options must state: "Molnupiravir use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. Merck will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with drug product distributed under this EUA for molnupiravir that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Merck will include in its notification to the Agency whether the batch, or batches, in question will be recalled.

If not included in its initial notification, Merck must submit information confirming that Merck has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Merck must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Merck will manufacture molnupiravir to meet all quality standards and per the manufacturing process and control strategy as detailed in Merck's EUA request. Merck will also test the active pharmaceutical ingredient (API) starting material for additional quality attributes agreed upon by Merck and the Agency. Merck will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

J. Through a process of inventory control, Merck and authorized distributor(s) will maintain records regarding distribution of molnupiravir (i.e., lot numbers, quantity, receiving site, receipt date).

K. Merck will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of Merck's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. Merck will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

L. FDA may require Merck to assess the activity of the authorized molnupiravir against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Merck will perform the required assessment in a manner and timeframe agreed upon by Merck and the Agency. Merck will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Merck will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

M. Merck shall provide samples as requested of molnupiravir to the U.S. Department of Health and Human Services (HHS) for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of molnupiravir may include, but are not limited to, cell culture potency assays, biochemical assays, and in vivo efficacy assays.

N. Merck must provide the following information to the Agency:

1. Merck will conduct a thorough investigation into the differences in efficacy observed in the first and second half of Part 2 of trial MK-4482-002. This assessment should involve the synthesis of data, including, but not limited to, additional baseline serology testing, a detailed comparison of baseline characteristics (including demographic, clinical disease, and virologic characteristics), and an exploration of potential differences in standard of care by region and over time. Merck will submit a report of its findings to the Agency. Merck will submit a preliminary report no later than March 31, 2022 and a final report incorporating available serology results no later than September 30, 2022.
2. Merck will submit the complete viral shedding results and full genome SARS-CoV-2 nucleotide sequencing results from the full randomized population in study MK-4482-002 Part 2. Viral sequencing analyses should include all Baseline and End-of-Treatment (Day 5) samples with sufficient RNA levels for analysis, as well as all Post-Treatment samples with viral

RNA levels ≥100,000 copies/mL. Cell culture infectivity assessments should be conducted for any clinical specimens in which amino acid changes were detected in the SARS-CoV-2 spike protein. Submissions should include summary report(s) and associated datasets (including analysis-ready datasets and raw fastq NGS data). A separate summary should be provided describing the results of the viral shedding and sequencing analyses specifically from immunocompromised patients. Merck will submit a preliminary report and associated datasets for the viral shedding and Baseline/Day 5 sequencing analyses no later than March 31, 2022, and a final report and datasets including the remaining analyses no later than June 30, 2022.

3. Merck will evaluate the cell culture antiviral activity of molnupiravir against an authentic SARS-CoV-2 isolate representative of the Omicron variant. Merck must submit a study report no later than February 28, 2022.
4. Merck will conduct a pharmacokinetic (PK) study in wild type Fisher 344 rats to establish if NHC or NHC-TP is detected in testes. The study should include plasma exposure levels that meet/exceed the human exposure for NHC. Merck will submit the results of the PK study no later than March 31, 2022.
    - If the results of the PK study demonstrate NHC or NHC-TP distribution to testes, Merck will also conduct a male germ cell mutation assay in the Big Blue rat model. Merck must submit a protocol for the Big Blue rat assay no later than 30 days after the PK results are submitted to FDA, or by April 30, 2022. Results from the Big Blue rat assay will be submitted no later than July 31, 2023.

O. Merck must maintain a pregnancy surveillance program to collect information through telephone and online reporting of pregnancies and collect outcomes for individuals who are exposed to molnupiravir during pregnancy. Merck must submit to the Agency reports detailing any available exposure information and outcome(s) data on a monthly basis unless otherwise notified by FDA.

P. Merck and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

<u>Healthcare Facilities to Whom Molnupiravir Is Distributed and Healthcare Providers Administering Molnupiravir</u>

Q. Healthcare facilities and healthcare providers will ensure that they are aware of the Letter of Authorization, and the terms herein. Healthcare providers must provide and document that a copy of the authorized Fact Sheet for Patients and Caregivers has been provided, either through electronic means or hardcopy, to the patient or caregiver prior to prescribing molnupiravir.

R. Healthcare providers must inform patients or caregivers of the information detailed in the section *Mandatory Requirements for Administration of Molnupiravir Under Emergency Use Authorization* in the Fact Sheet for Healthcare Providers.

S. Molnupiravir may only be prescribed to a pregnant individual after the prescribing healthcare provider has completed the mandatory requirements on patient assessment, patient counseling, and documentation as described in the Fact Sheet for Healthcare Providers. See *Mandatory Requirements for Administration of Molnupiravir Under Emergency Use Authorization* in the Fact Sheet for Healthcare Providers.

T. Healthcare providers must inform and document that pregnant individuals who are prescribed molnupiravir have been made aware of Merck's pregnancy surveillance program as detailed in the authorized Fact Sheets. If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing healthcare provider to disclose patient specific information to Merck, the prescribing healthcare provider must provide the patient's name and contact information to Merck at 1-877-888-4231 or pregnancyreporting.msd.com.

U. Healthcare facilities and healthcare providers receiving molnupiravir will track all medication errors and serious adverse events that are considered to be potentially attributable to molnupiravir use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports must state, "Molnupiravir use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis. A copy of the completed FDA Form 3500 must also be provided to Merck per the instructions in the authorized labeling.

V. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.

W. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of molnupiravir for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

X. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Merck and/or FDA. Such records will be made available to Merck, HHS, and FDA for inspection upon request.

Y. Healthcare facilities and providers will report therapeutics information and utilization data as directed by HHS.

Conditions Related to Printed Matter, Advertising, and Promotion

Z. All descriptive printed matter, advertising, and promotional materials relating to the use of molnupiravir under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling" or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of molnupiravir under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 at the time of initial dissemination or first use.

If the Agency notifies Merck that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions Z through BB of this EUA, Merck must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Merck to issue corrective communication(s).

AA. No descriptive printed matter, advertising, or promotional materials relating to the use of molnupiravir under this authorization may represent or suggest that molnupiravir is safe or effective when used for the treatment of COVID-19.

BB. All descriptive printed matter, advertising, and promotional material, relating to the use of molnupiravir under this authorization clearly and conspicuously shall state that:

- Molnupiravir has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate; and

- The emergency use of molnupiravir is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

Page 11 – Merck Sharp & Dohme Corp.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

/s/

Jacqueline A. O'Shaughnessy, Ph.D.
Acting Chief Scientist
Food and Drug Administration

Dated: January 28, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022–02359 Filed 2–3–22; 8:45 am]

BILLING CODE 4164–01–C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Agency Information Collection Activities: Submission to OMB for Review and Approval; Public Comment Request; The Stem Cell Therapeutic Outcomes Database, OMB No. 0915–0310—Extension

AGENCY: Health Resources and Services Administration (HRSA), Department of Health and Human Services.

ACTION: Notice.

SUMMARY: In compliance with of the Paperwork Reduction Act of 1995, HRSA has submitted an Information Collection Request (ICR) to the Office of Management and Budget (OMB) for review and approval. Comments submitted during the first public review of this ICR will be provided to OMB. OMB will accept further comments from the public during the review and approval period. OMB may act on HRSA's ICR only after the 30 day comment period for this Notice has closed.

DATES: Comments on this ICR should be received no later than March 7, 2022.

ADDRESSES: Written comments and recommendations for the proposed information collection should be sent within 30 days of publication of this notice to *www.reginfo.gov/public/do/PRAMain.* Find this particular information collection by selecting ''Currently under Review—Open for Public Comments'' or by using the search function.

FOR FURTHER INFORMATION CONTACT: To request a copy of the clearance requests submitted to OMB for review, email Samantha Miller, the acting HRSA Information Collection Clearance Officer at *paperwork@hrsa.gov* or call (301) 443–9094.

SUPPLEMENTARY INFORMATION:

Information Collection Request Title: The Stem Cell Therapeutic Outcomes Database OMB No. 0915–0310—Extension.

Abstract: Given the rapid evolution of COVID–19 and its impact on those with compromised immune systems, it is imperative for the transplant community to continue collecting COVID–19 related data. Having access to COVID–19 vaccination status on blood stem cell recipients and understanding immune responses will assist with making informed decisions regarding direct clinical care. This will also inform critical policy decisions.

The Stem Cell Therapeutic and Research Act of 2005, Public Law (Pub. L.) 109–129, as amended, provides for the collection and maintenance of human blood stem cells for the treatment of patients and research. It also maintains a scientific database of information relating to patients who have been recipients of a stem cell therapeutics product (*e.g.,* bone marrow, cord blood, or other such product) from a donor.

Given the rapid evolution of the COVID–19 public health emergency and its impact on immunocompromised patients, availability of new vaccines, and continual changes in vaccination recommendations, HRSA wants to leverage the required data collection platform of the Stem Cell Therapeutic Outcomes Database to obtain vaccine information for all US allogeneic hematopoietic stem cell transplant recipients.

A 60-day notice published in the **Federal Register**, 86 FR 67478 (November 26, 2021). There were no public comments.

Need and Proposed Use of the Information: To collect COVID–19 vaccine data, HRSA is requesting an extension of OMB's approval of both the Pre-Transplant Essential Data (Pre-TED) Form 2400 and Post-Transplant Essential Data (Post-TED) Form 2450. Collecting these data will help clinicians and policymakers to understand the landscape of vaccination among immunocompromised patients before and after a blood stem cell transplant.

This information will be used to analyze outcomes based on vaccine manufacturer/type, doses received (including potential boosters), timing, and inform future vaccination strategies. Information currently collected regarding COVID–19 infections has already been used in research studies.

Data collected prior to a patient receiving a blood stem cell transplant will be used to characterize frequencies of vaccination, and the level of protection afforded during and after transplant based on the incidence of COVID infection. Post-transplant, this information can be used to assess vaccination rates and timing in blood stem cell recipients, characterize emerging vaccination strategies (which may include ''boosters''), describe possible short and long-term side effects