June 23, 2023

The Honorable Dan Crenshaw
U.S. House of Representatives
Washington, D.C. 20515

Dear Representative Crenshaw:

Thank you for your letter of May 3, 2023, cosigned by Rep. Lori Trahan, to the Food and Drug Administration (FDA or the Agency) regarding Agency review of COVID-19 therapeutics. We appreciate your continued interest in this topic.

Initially created in April 2020, FDA's Coronavirus Treatment Acceleration Program (CTAP) worked closely with sponsors to accelerate the study of potentially beneficial therapies for the prevention or treatment of COVID-19. CTAP enabled the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) to leverage cross-agency scientific resources and expertise for COVID-19 therapeutic development and review and provide extensive guidance and information to companies, researchers, patients, and consumers.

CTAP helped FDA achieve numerous critical milestones in the COVID-19 response. For example, FDA issued 19 Emergency Use Authorizations (EUAs) covering drugs or non-vaccine biological products for the prevention or treatment of COVID-19.[1] The EUAs covered myriad drug classes, including direct acting antivirals, SARS-CoV-2 targeting monoclonal antibodies, and immunomodulators, and authorized uses for either the prevention or treatment of COVID-19, which collectively, spanned the full spectrum of symptomatic disease.

FDA also approved four drug treatments for COVID-19. In October 2020, FDA approved the first antiviral drug, Veklury (remdesivir), an intravenous therapy, for the treatment of COVID-19 in certain hospitalized adults.[2] Based on FDA's subsequent approval of supplemental applications, Veklury is now approved for use in both hospitalized and non-hospitalized settings. In hospitalized patients, Veklury decreases patients' time to recovery; in non-hospitalized patients, Veklury reduces the risk of progression to severe disease, including hospitalization or death. Most recently, FDA approved Paxlovid, an oral antiviral drug, 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.[3] Based on data from clinical trials, patients treated with Paxlovid were 86 percent less likely to be hospitalized or die from COVID-19 when compared to patients who received placebo. FDA also approved the immune

[1] For a current list of EUAs covering COVID-19 treatments, please refer to FDA's website at https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

[2] For additional information on FDA's initial approval of Veklury, please see https://www.nejm.org/doi/10.1056/NEJMp2032369

[3] For additional information on FDA's approval of Paxlovid, please see https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-antiviral-treatment-covid-19-adults

modulators Olumiant (baricitinib) and Actemra (tocilizumab) for the treatment of certain hospitalized adults with COVID-19.

As noted in your letter, the monoclonal antibody therapies targeting SARS-CoV-2 previously made available under EUA are not currently authorized in the United States until further notice by the Agency. This is a result of the relatively high prevalence of viral variants of SARS-CoV-2, which contain changes in the receptor binding domain of the virus, circulating within the United States. Such changes in the virus have greatly impacted the activity of these monoclonal antibody therapies.

New products, particularly those with conserved targets that are less susceptible to changes in SARS-CoV-2, are needed to help ensure that safe and effective therapies for the prevention or treatment of COVID-19 remain viable well into the future. The development of COVID-19 therapeutics that are effective against current and future variants remains a priority.

CTAP today remains vital to the expedited development of COVID-19 therapeutics, particularly for programs that are intended to address an unmet medical need. Using available regulatory mechanisms, CTAP strives to facilitate access to safe, effective, and high-quality treatments for COVID-19. CTAP is leveraging the Agency's scientific experience and knowledge of COVID-19 to support current and future clinical trials testing new treatments for COVID-19. From these efforts, FDA continues to gain valuable knowledge about the safety and effectiveness of potential therapies for COVID-19.

Below are the Agency's responses to the specific questions raised in your letter:

1. Will the FDA consider a platform approach for authorizing and approving updated mAbs or antivirals?

FDA is working closely with sponsors to facilitate development of monoclonal antibodies (mAbs) that retain activity against currently circulating variants to address immediate unmet needs, and to facilitate development of new products with conserved targets that are less susceptible to changes in SARS-CoV-2.

As described below, FDA has leveraged knowledge from the Agency's extensive experience with mAbs in expediting the development and authorization of mAbs for COVID-19. We anticipate continuing to apply this approach for updated mAbs to streamline development, particularly for products that may meet an unmet need.

For example, the chemistry, manufacturing, and controls (CMC) development of neutralizing mAbs to treat COVID-19 was abbreviated based on the Agency's over 20 years of experience in regulating mAbs for serious and life-threatening conditions, as outlined in the 1997 guidance "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use."[4] This guidance outlines abbreviated steps sponsors can use to get products for the treatment of serious and life-threatening conditions into clinical trials faster. Note that this guidance was the first to endorse what would eventually become known as a "platform process" by promoting a "generic and

[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/points-consider-manufacture-and-testing-monoclonal-antibody-products-human-use

modular virus clearance" approach. Monoclonal antibodies authorized for the treatment of COVID-19 commonly use these abbreviated approaches for CMC development. The concepts in this guidance were also applied to the Agency's experience in regulating newer aspects of the manufacturing and development of mAbs that were developed after the issuance of the guidance document. Our experience leveraging data for mAbs was also included in the more recent guidance, *Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency Guidance for Industry*.[5]

2. In the 117th Congress, language creating a platform designation program for technologies reviewed by the FDA was signed into law. Is the FDA open to utilizing this directive for the review of products that treat and prevent COVID-19, including products previously under EUA?

To be eligible for designation, a platform technology must be used in an approved application. EUAs are not approved applications. Thus, a platform limited to authorization under EUA would not be eligible for this designation. If the COVID-19 therapeutic utilizes a platform technology that has been used in another approved product, the platform could be eligible for designation if the other statutory criteria for designation are met.

3. While mAbs and antivirals are often prescribed to patients who are at high risk for hospitalization or death from COVID-19, there are still gaps in the availability of these drugs that contribute to poorer patient outcomes. How is the FDA currently working with health care providers to identify supply chain and delivery barriers and find solutions to them?

As noted above, the monoclonal antibody therapies targeting SARS-CoV-2 previously made available under EUA are not currently authorized in the United States until further notice by the Agency. This is a result of the relatively high prevalence of viral variants of SARS-CoV2, which contain changes in the receptor binding domain of the virus circulating within the United States. Such changes in the virus have greatly impacted the activity of these monoclonal antibody therapies. The remaining portion of this question would be best answered by the Administration for Strategic Preparedness and Response (ASPR) which is directing the distribution of the currently authorized oral antivirals – Veklury (remdesivir) is distributed by Gilead.

4. Does streamlining the clinical data package make sense for updated treatment and prevention options, particularly for targeted populations with unmet medical need and high risk of poor outcomes?

The Agency will exercise flexibility when appropriate regarding updates to a development program while ensuring that the relevant legal standards for safety and effectiveness are met. We continue to encourage sponsors to engage with the Agency

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-monoclonal-antibody-products-targeting-sars-cov-2-including-addressing-impact-emerging

early and often regarding the development of potential therapies for the treatment or prevention of COVID-19.

5. Recognizing that many of these therapeutics are aimed at a high-risk patient population with the highest likelihood of benefits, what recent changes have been made to expedite the authorization process?

In addition to the numerous efforts described above to streamline the development of therapeutics for COVID-19, in February 2021, the Agency provided guidance to industry on how to efficiently generate non-clinical and chemistry, manufacturing and controls data to streamline moving new monoclonal antibody products that may be effective against emerging variants into clinical trials (See Guidance for Industry *Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency*).

In December 2022, FDA and the European Medicines Agency (EMA) conducted a workshop to discuss strategies to expedite the development of monoclonal antibodies in the setting of rapidly changing variants. This included a discussion of alternative strategies to support the development of novel monoclonal antibody therapies, particularly those targeted to patient populations with an unmet medical need. We continue to work closely with sponsors interested in applying these approaches to their products to support requests for emergency use authorization.

Thank-you again for your interest in FDA's efforts to expedite the development and availability of COVID-19 therapeutics. We have sent the same letter to your cosigner.

Sincerely,

Kimberlee R. Trzeciak -S

Digitally signed by Kimberlee R. Trzeciak -S
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Kimberlee Trzeciak
Associate Commissioner for
Legislative Affairs