November 21, 2020

Ms. Emily Miner
Vice President, Global Quality and Regulatory
Terumo Cardiovascular 6200 Jackson Road
Ann Arbor, MI 48103

Dear Ms. Miner:

This letter is in response to your request on behalf of Terumo Cardiovascular, that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of the CAPIOX Emergency Bypass System[1] (hereafter "CAPIOX EBS") to be used by healthcare providers (HCP)[2] in the hospital setting to provide long-term (> 6 hours) respiratory or cardiopulmonary support to treat patients 18 years or older with Coronavirus Disease 2019 (COVID-19) who have acute respiratory failure or acute cardiopulmonary failure, where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent.

On February 4, 2020, pursuant to section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (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 COVID-19.[3] Pursuant to section 564 of the Act, and on the basis of such determination, the Secretary of HHS then declared on March 24, 2020, that circumstances exist justifying the authorization of emergency use of medical devices, including alternative products used as

[1] The CAPIOX EBS is an extracorporeal membrane oxygenation (ECMO) system, regulated under 21 CFR 870.4100. The authorized device consists of the following components: (1) the CAPIOX EBS Circuit with X Coating (a kit consisting of a membrane oxygenator with microporous polymethylpentene (PMP) hollow fibers, a centrifugal pump, and blood tubing); (2) the CAPIOX Centrifugal Pump Controller (a console that controls and drives the disposable centrifugal pump in the CAPIOX EBS Circuit); and (3) the CAPIOX EBS Cannula Kit with X Coating (a kit consisting of cannulas used to connect the blood vessels to the circuit and supporting tools for catheterization, including one cannula, one dilator, one entry needle, one guide wire, pre-dilators, one syringe, and one scalpel). The CAPIOX EBS is currently approved and marketed in Japan, Taiwan, South Korea, and Vietnam. The CAPIOX EBS is not cleared or approved in the United States.

[2] For purposes of this letter, healthcare providers (HCP) refers to healthcare professionals in critical care, intensive care, emergency medicine, emergency response, cardiology, or anesthesiology that are trained to provide ECMO therapy.

[3] 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*. 85 FR 7316 (February 7, 2020).

medical devices, due to shortages during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.[4]

The severe acute respiratory syndrome (SARS) due to COVID-19 can trigger acute respiratory and/or acute cardiopulmonary failure. Under such conditions, Extracorporeal Membrane Oxygenation (ECMO) therapy, or long-term extracorporeal oxygenation (i.e., extracorporeal oxygenation for greater than 6 hours), is being used to treat patients with COVID-19 infection. While FDA-approved or cleared cardiopulmonary bypass (CPB) devices, intended for extracorporeal oxygenation for less than 6 hours, are being used clinically for ECMO therapy, they are not FDA-approved or cleared for such use.[5] In addition, there is one alternative FDA-cleared full ECMO system that is not widely in distribution at this time, and one FDA-cleared oxygenator module which is a component of an ECMO system[6]. However, based on disease projection models driving increased demand, there are not adequate, available supplies of these FDA-approved or cleared alternatives available during the COVID-19 pandemic.[7] Therefore, FDA has determined that there is no adequate, approved, and available alternative to this device for treating COVID-19.

Based on the available scientific information, including design verification, validation studies performed, and the clinical experience of the device in Japan, Taiwan, South Korea, and Vietnam as shown in postmarket vigilance reports received and literature search conducted by the manufacturer, FDA has concluded that the CAPIOX EBS may be effective at treating COVID-19 by providing long-term (> 6 hours) respiratory or cardiopulmonary support to treat patients 18 years or older with COVID-19 who have acute respiratory failure or acute cardiopulmonary failure, and who have failed other treatment options and are expected to continue to deteriorate, or for whom the risk of death is imminent.

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 the CAPIOX EBS, as described in the Scope

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[4] 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 17335 (March 27, 2020).

[5]Cardiopulmonary bypass (CPB) devices FDA-cleared for use for up to 6 hours during open-heart surgery are being repurposed for ECMO therapy under certain circumstances during the COVID-19 emergency. FDA issued Guidance on April 6, 2020, that outlines an enforcement discretion policy for such use. For more information about this policy, please see 'Enforcement Policy for Extracorporeal Membrane Oxygenation and Cardiopulmonary Bypass Devices During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency'. < https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-extracorporeal-membrane-oxygenation-and-cardiopulmonary-bypass-devices-during>

[6] There is one alternative full ECMO system that is FDA-cleared under K191407. There is also an oxygenator module for use as a component in a system intended to provide ECMO therapy that is FDA-cleared under K191935.

[7] Based on the available information, including information on the FDA-cleared full ECMO system which shows limited distribution in the United States, data supporting the use of repurposed CPB devices being used to meet the current ECMO therapy need (indicating that the market is filling the need for ECMO devices using CPB devices outside their cleared labeling, which is contributing to underestimating the actual supply issues and demand for FDA-cleared or approved devices intended for ECMO therapy at this time), and projection models for COVID-19 cases and ECMO device demand provided by the sponsor and verified by FDA using external sources, FDA has determined that the cleared ECMO devices referenced in footnote 6, are not adequately available because of increased demand for such devices to treat patients with COVID-19.

of Authorization (Section II) and pursuant to the Conditions of Authorization (Section III) of this letter.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the CAPIOX EBS, as described in the Scope of Authorization (Section II) of this letter meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

1. SARS-CoV-2, the disease that causes COVID-19, 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 the CAPIOX EBS may be effective in treating COVID-19 by providing long-term (> 6 hours) respiratory or cardiopulmonary support to treat patients 18 years or older with COVID-19 who have acute respiratory failure or acute cardiopulmonary failure where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent, and that the known and potential benefits of the CAPIOX EBS for such use, outweigh the known and potential risks; and,

3. There is no adequate, approved, and available alternative to the emergency use of the CAPIOX EBS when there are shortages of FDA-cleared alternatives during the COVID-19 pandemic.[8]

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the CAPIOX EBS by HCP in the hospital setting for providing long-term (> 6 hours) respiratory or cardiopulmonary support to treat patients 18 years or older with COVID-19 who have acute respiratory failure or acute cardiopulmonary failure, and who have failed other available treatment options and are expected to continue to clinically deteriorate, and for whom the risk of death is imminent.

The CAPIOX EBS must not be used for patients with the following conditions:

- Known heparin sensitivity
- With placement of an inferior vena cava filter.

<u>The Authorized CAPIOX EBS</u>

The CAPIOX EBS is an ECMO system for long-term respiratory or cardiopulmonary failure.

[8] No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

The CAPIOX EBS is comprised of the following components:

- The CAPIOX EBS Circuit with X Coating: Item codes CX*XSA (with SP45 centrifugal pump, arterial and venous length 1.2m each, with EBS Lock Connector); CX*XSA0171 (with SL45 centrifugal pump, arterial and venous length 1.7m each, with EBS Lock Connector); CX*XSA0251 (with SL45 centrifugal pump, arterial and venous length 2.5m each, with EBS Lock Connector); and CX*XSA0173 (with SL45 centrifugal pump, arterial and venous length 1.7m each, no EBS Lock Connector).
- The CAPIOX Centrifugal Pump Controller: Item codes: ME*SP200C (Centrifugal Pump Controller SP-200, power plug American type); ME*SP200M (Drive Motor); ME*SPFAS01 (ABD/Flow Sensor); XX*SPCBL011 (Temp Sensor Cable, Blue); XX*SPCBL012 (Temp Sensor Cable, Red); XX*SPCBL021 (Pressure Sensor Cable); XX*SPCBL031 (CDI Communication Cable); XX*SP05 (Hand Crank); and XX*EB04 (Dedicated CAPIOX EBS LX Holder).
- The CAPIOX EBS Cannula Kit – A kit consisting of cannulas used to connect the blood vessels to the circuit and supporting tools for catheterization, including one cannula, one dilator, one entry needle, one guide wire, pre-dilators, one syringe, and one scalpel. The blood contacting surface of the cannula is coated with X coating.

The above described CAPIOX EBS, is authorized to be accompanied with labeling, entitled "CAPIOX Emergency Bypass System Instructions for Use" (available at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations), together with the following product-specific information pertaining to emergency use, which is required to be made available to HCP and patients, respectively:

- Fact Sheet for Healthcare Providers: Emergency Use of CAPIOX Emergency Bypass System During the COVID-19 Pandemic
- Fact Sheet for Patients: Emergency Use of CAPIOX Emergency Bypass System During the COVID-19 Pandemic

The above described product, when accompanied with the CAPIOX Emergency Bypass System Instructions for Use (identified above) and the two Fact Sheets (referred to as "authorized labeling") is authorized to be distributed under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

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 the CAPIOX EBS when used consistent with the Scope of Authorization of this letter (Section II), outweigh the known and potential risks of this product.

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 the authorized CAPIOX EBS may be effective when used consistent with the Scope of Authorization of this letter (Section II), pursuant to section 564(c)(2)(A) of the Act.

FDA has reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above**Error! Reference source not found.**, and concludes that the authorized CAPIOX EBS, as described in the Scope of Authorization of this letter (Section II), meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the CAPIOX EBS must be consistent with, and may not exceed, the terms of this letter, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms and conditions 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), the CAPIOX EBS described above is authorized for use by HCP in the hospital setting for providing long-term (> 6 hours) respiratory or cardiopulmonary support to treat patients 18 years or older with COVID-19 who have acute respiratory failure or acute cardiopulmonary failure where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent.

III. Conditions of Authorization

Pursuant to section 564(e) of the Act, I am establishing the following conditions on this authorization:

Terumo Cardiovascular, as Sponsor of the Authorized Product

A. Terumo Cardiovascular must comply with the labeling requirements under 21 CFR 801 Subpart A (general labeling provisions) and 21 CFR 801.109 (labeling for prescription devices), as well as those described in Section II of this letter, Scope of Authorization. Compliance with unique device identification regulations (see Subpart B of 21 CFR Part 801) is not required under this EUA.

B. Terumo Cardiovascular must comply with applicable current good manufacturing practice requirements, including quality system requirements under 21 CFR Part 820 with respect to the design, manufacture, packaging, labeling, storage, and distribution of the authorized devices.

C. Terumo Cardiovascular will make the CAPIOX EBS available with authorized labeling. Terumo Cardiovascular may request changes to the authorized labeling. Such changes require review and concurrence from OHT2/OPEQ/CDRH.

D. Terumo Cardiovascular may request changes to this authorization, including to the authorized Fact Sheets, that do not alter the analysis of benefits and risks that underlies this authorization and FDA may determine that such changes may be permitted without amendment of this EUA. That determination must be made by joint decision of OHT2/OPEQ/CDRH and the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC).

E. Terumo Cardiovascular must have processes and adequate Medical Device Reporting procedures in place in accordance with 21 CFR Part 803, and must to report to FDA all adverse events of which Terumo Cardiovascular becomes aware related to the CAPIOX EBS in accordance with 21 CFR Part 803. Terumo Cardiovascular must also establish a process to collect adverse event information from healthcare facility customers.

F. Terumo Cardiovascular must notify FDA of any authorized distributor(s)[9] of the CAPIOX EBS, including the name, address, and phone number of any authorized distributor(s), and provide authorized distributor(s) with a copy of this EUA and any updates.

Terumo Cardiovascular and any Authorized Distributor(s)

G. Terumo Cardiovascular and authorized distributors must distribute the CAPIOX EBS with the authorized labeling only to healthcare facilities with HCP who are adequately equipped, trained, and capable of using the CAPIOX EBS according to the authorized labeling.

H. Terumo Cardiovascular and authorized distributors must make the authorized labeling available on their websites.

I. Authorized distributors must make Terumo Cardiovascular aware of any adverse events of which they become aware.

J. Through a process of inventory control, Terumo Cardiovascular and authorized distributors must maintain records of the healthcare facilities to which they distribute the CAPIOX EBS and the number of products they distribute.

K. Terumo Cardiovascular and authorized distributor(s) are authorized to make available additional information relating to the emergency use of the product that is consistent with, and does not exceed, the terms of this letter of authorization.

L. Terumo Cardiovascular and authorized distributor(s) must ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

Healthcare Facilities

M. Healthcare facilities using the CAPIOX EBS must make available to patients the accompanying Patient Fact Sheet and make available to the HCP the accompanying Healthcare Provider Fact Sheet and Instructions for Use.

[9] "Authorized Distributor(s)" are identified by Terumo Cardiovascular in an EUA submission as an entity allowed to distribute the device.

N. Healthcare facilities using the CAPIOX EBS must make Terumo Cardiovascular, and FDA aware of any adverse events in accordance with 21 CFR Part 803.

O. Healthcare facilities must ensure HCP using the CAPIOX EBS are adequately equipped, trained, and capable of device usage, and will maintain records of device usage.

Conditions Related to Printed Materials, Advertising and Promotion

P. All descriptive printed matter, advertising, promotional materials, relating to the use of the CAPIOX EBS shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

Q. No descriptive printed matter, advertising, or promotional materials, relating to the use of the CAPIOX EBS may represent or suggest that this product is safe or effective for providing long-term (> 6 hours) respiratory or cardiopulmonary support to treat patients18 years or older with COVID-19 who have acute respiratory failure or acute cardiopulmonary failure where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent.

R. All descriptive printed matter, advertising, and promotional materials, relating to the authorized use of the CAPIOX EBS shall clearly and conspicuously state that:

- The CAPIOX EBS has neither been cleared or approved for providing long-term (> 6 hours) respiratory or cardiopulmonary support to treat patients 18 years or older with COVID-19 who have acute respiratory failure or acute cardiopulmonary failure where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent;

- The CAPIOX EBS has been authorized for emergency use by FDA under an EUA; and,

- The CAPIOX EBS has been authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of medical devices under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the CAPIOX EBS is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

Sincerely,

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RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures