April 9, 2020

Ms. Janet Johnson
Terumo BCT, Inc.
10811 W. Collins Avenue
Lakewood, CO 80215

Dear Ms. Johnson:

This letter is response to a request from the Biologics & Medical Device Consulting Group on behalf of Terumo BCT, Inc. and Marker Therapeutics AG that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of the Spectra Optia Apheresis System[1] with the Depuro D2000 Adsorption Cartridge (also referred to as an extracorporeal blood purification (EBP) device) to treat patients 18 years of age or older with confirmed Coronavirus Disease 2019 (COVID-19) admitted to the intensive care unit (ICU) with confirmed or imminent respiratory failure to reduce pro-inflammatory cytokines levels, 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 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.[2] 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 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.[3]

[1] The Spectra Optia® Apheresis System is a 510(k) cleared product, with most recent clearance for this device obtained on November 30, 2018 (K183081) under product code LKN – Separator, Automated, Blood Cell and Plasma, Therapeutic. The authorized emergency use of this device, the Spectra Optia Apheresis System with a Secondary Plasma Device (SPD) is largely identical to the K183081 device, with the exception that the authorized product under this EUA has a software option to allow the flow of plasma through an SPD. The SPD-enabled Spectra Optia authorized product only entails a software change from the cleared therapeutic plasma exchange (TPE) device. As such, this system introduces no new hardware or disposable related risks. The overall strategy to manage the plasma/cellular interface and to separate plasma has not changed from the 510(k) cleared system.

[2] 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).

[3] 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).

There are no FDA approved, licensed, or cleared device treatments for COVID-19. Based on a number of tests and clinical case series, FDA has concluded that the unapproved use of the cleared Spectra Optia Apheresis System may effectively separate plasma from whole blood, and the Depuro D2000 Adsorption Cartridge may remove various pro-inflammatory cytokines from that plasma. FDA believes based on the totality of scientific evidence available, that the removal of pro-inflammatory cytokines may ameliorate cytokine storm due to the overabundance of pro-inflammatory cytokines and, in turn, provide clinical benefit.

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 Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge as described in the Scope of Authorization (Section II) of this letter, subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge as described in the Scope of Authorization (Section II) of this letter to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure 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 virus 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 Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge may be effective in treating patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure, and that the known and potential benefits of the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge, when used to treat COVID-19 patients 18 years of age or older, outweigh the known and potential risks of the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge; and

3. There is no adequate, approved, and available alternative to the emergency use of the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge for the treatment of these COVID-19 patients.[4]

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 Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure by reducing pro-inflammatory cytokine levels which may ameliorate a cytokine storm due to the overabundance of pro-inflammatory cytokines and, in turn, provide clinical benefit to such patients. For the purposes of this EUA, a

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

patient with confirmed COVID-19 who is admitted to the ICU with confirmed or imminent respiratory failure is a patient 18 years of age or older who has any one of the following conditions:

a) Early acute lung injury (ALI)/early acute respiratory distress syndrome (ARDS); or
b) Severe disease, defined as:
    1) dyspnea,
    2) respiratory frequency ≥ 30/min,
    3) blood oxygen saturation ≤ 93%,
    4) partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
    5) lung infiltrates > 50% within 24 to 48 hours; or
c) Life-threatening disease, defined as:
    1) respiratory failure,
    2) septic shock, and/or
    3) multiple organ dysfunction or failure.

Authorized Product Details

1. The Depuro D2000 Adsorption Cartridge is comprised of the following components and materials:

Component Description	**Materials of Construction**
Resin	AMBERLITE XAD7HP
Resin	AMBERCHROM CG300
Resin	Activated Carbon from Virgin Coconut Shells
Filter pad	Polypropylene
Cartridge Housing	MAKROLON 2658 Polycarbonate

2. The Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge devices mechanisms of function are as follows:

    The D2000 Adsorption Cartridge operates in conjunction with the Terumo Spectra Optia device. The D2000 Adsorption Cartridge is integrated into the extracorporeal circuit, downstream from where the plasma is separated, into the Secondary Plasma Device (SPD) position of the circuit. After priming the D2000 Adsorption Cartridge and assembling the inlet and outlet lines to the plasma circuit, plasma filtration can be run for up to 4 hours, to be repeated as needed.

    The D2000 Adsorption Cartridge contains activated uncoated coconut shell (carbon granules) charcoal (100 gm), and the nonionic resins Amberlite XAD-7HP and Amberchrom GC300C. These adsorption materials have been demonstrated to be

efficacious in the removal of statistically significant proportions of IL-3, IFN-gamma, IL-10, IL-1B, IL-6, IL-8, MCP-1, and TNF-alpha when compared to control. The adsorbents attract solutes through a variety of forces, including hydrophobic interactions, ionic (or electrostatic) attraction, hydrogen bonding, and van der Waals interactions.

Management of the cytokine storm and cascade associated with COVID-19 whilst treating the underlying pathogenesis may decrease patient morbidity. The reduction of cytokines must be done in a discrete, controlled fashion, to balance the patient's immune response to the infection with the removal of the excess inflammatory cascade. Therefore, therapy with the D2000 will be administered for up to 4 hours per day.

The Spectra Optia® Apheresis System Equipment (61000) is a non-patient, non-fluid contacting device.

The Spectra Optia® Exchange Sets (12220, 10220) are comprised of the following components and materials:

Spectra Optia Exchange Set	**Part Name**	**Key Function**	**Raw Materials** **Contact with Human Body** **(D)** – Direct / **(I)** – Indirect
	Inlet line	Used to carry anticoagulated blood from the patient to the channel	• Polypropylene (I) • PVC (D) • Polycarbonate (D) • Paper (I) • Acrylic (I)
	Inlet line manifold	Provides a connection point for the inlet line, the AC line, and the inlet saline line. Includes an injection port	• DCTG (D) • C-Flex (D)
	Inlet saline line clamp	Used to close the inlet saline line or to control the flow of saline to the patient.	• ABS (I)
	AC check valve	Allows the system to pump AC through the tubing but prevents the free flow of AC.	• Acrylic (D) • Silicon (D)
	Return line	Used to carry fluid from the reservoir to the patient	• Polypropylene (I) • PVC (D) • Polycarbonate (D) • Paper (I) • Acrylic (I)
	Return line manifold	Provides a connection point for the return line and the return saline line.	• Silicon (D) • Copolyester (D)
	Return saline line clamp	Used to close the return saline line or to control the flow of saline to the patient.	• ABS (I)
	Anticoagulant (AC) line	Used to carry AC from the AC container to the inlet line manifold	• High Density Polyethylene (HDPE)(I) • ABS (D) • Polycarbonate (D)

			• Acrylic (D) • Polyethersulfone (PTFE) (D)
	Saline line	Used to carry saline from the saline container to the inlet line manifold and the return line manifold	• ABS (D) • PVC (D) • Polyethylene (I) • Low Density Polyethylene (LDPE) (I) • Polypropylene (I)
	Inlet line trap	Prevents larger solid cellular matter from entering the channel	• Polypropylene (D)
	Inlet pressure sensor Diaphragm	Attaches to the inlet pressure sensor on the front panel to monitor pressure in the inlet line.	• Silicon (D) • Loctite 3201 (I) • Steel (I) • Nickel (I)
	Centrifuge pressure sensor Diaphragm	Attaches to the centrifuge pressure sensor on the front panel to monitor pressure in the channel and the lines in the centrifuge.	• Silicon (D)
	Reservoir	Used to hold the fluid that is returned to the patient	• Copolyester (D) • PVC (D) • Polyester (D)
	Cassette	guides the flow of blood and products through the tubing set.	• Copolyester (D) • Polyethylene (D) • PVC (D) • Paper (I) • Acrylic (I) • Wax/Resin (Ink) (I)
	Return pressure sensor Diaphragm	Attaches to the return pressure sensor on the front panel to monitor pressure in the return line	• Silicon (D) • Loctite 3201 (I) • Steel (I) • Nickel (I)
	Centrifuge loop	Consists of lines that are loaded in the centrifuge	• PVC (D) • Polyurethane (I) • Acetal (I) • Polyethylene (D) • Terephthalate (PET) (I)
	Channel	Used during centrifugation to separate the patient's blood into cellular components.	• PVC (D)
	Connector	Secures the lines where the separated components exit the channel.	• PVC (D)
	Vent bag	Holds air that is displaced from the system.	• PVC (D)
	Remove bag	Holds removed blood components.	• PVC (D)
	Remove line	Used to carry removed blood components to the remove bag.	• PVC (D) • Copolyester (D)

	Extra remove line	Used to carry removed blood components to an extra remove bag, if connected	• PVC (D) • Polycarbonate (D) • HDPE (D)
	Replace line	Used to carry replacement fluid from the replacement fluid container to the reservoir.	• PVC (D) • Polycarbonate (D) • ABS (D) • Polyethylene (I) • Low Density Polyethylene (LDPE) (I) • Polypropylene (I)

3. The following device settings have been validated for operation of the D2000 Adsorption Cartridge with the Terumo Spectra Optia with SPD software:

    - Prime divert volume: 200 mL
    - Notification pressure limit: 200 mmHg
    - Maximum pressure limit: 300 mmHg
    - Maximum plasma flow rate: 50 mL/min

    Prime can be performed at up to 100 mL/min. At the start of treatment, the plasma pump flow rate may be adjusted up to 25 mL/min for the first 250 mL of plasma processed. Then, the plasma flow rate may be increased up to 50 mL/min as needed. This may be managed by the physician to operate between 15 and 50 mL/min, maintaining a pressure drop over the D2000 of less than 300 mmHg. This information has been provided in the Operation Manual for Use of the Depuro D2000 Adsorption Cartridge with the Terumo Spectra Optia™ Apheresis System, provided with this EUA as.

The Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge, when labeled consistently with the labeling authorized by FDA, entitled "Operation Manual for Use of D2000 with the Spectra Optia Apheresis System," "Spectra Optia Apheresis System Operator's Manual," and "D2000 Cartridge Instructions for Use" (available at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations), which may be revised in consultation with, and with concurrence of, the Division of Renal, Gastrointestinal, Obesity and Transplant Devices (DHT3)/Office of GastroRenal, ObGyn, General Hospital and Urology Devices (OHT3)/Office of Product Evaluation and Quality (OPEQ)/Center for Devices and Radiological Health (CDRH), is authorized under the terms and conditions of this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

The Spectra Optia device and the Depuro D2000 Adsorption Column are authorized to be accompanied by the following product-specific information pertaining to the emergency use, which is required to be made available to healthcare providers and patients:

- Fact Sheet for Healthcare Personnel: Emergency Use Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge for COVID-19

- Fact Sheet for Patients: Emergency Use of Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge for 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 the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge used to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure, when used consistently 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 Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge may be effective in treating patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure, when used consistently 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, and concludes that the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge, when used to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure (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 authorized products under this EUA 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 IV). 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), the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge, with the required labeling set forth in this section (Section II), is authorized to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure, by reducing cytokine levels (associated inflammatory response).

This EUA will cease to be effective when the HHS declaration that circumstances exist to justify the EUA is terminated under section 564(b)(2) of the Act or when the EUA is revoked under section 564(g) of the Act.

III. Waiver of Certain FDA Requirements

I am waiving applicable current good manufacturing practice requirements, including the quality system requirements under 21 CFR Part 820 with respect to the design, manufacture, packaging, labeling, storage, and distribution of the authorized devices that are used in accordance with this EUA.

IV. Conditions of Authorization

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

Terumo BCT, Inc. and Marker Therapeutics AG

A. Terumo BCT, Inc and Marker Therapeutics AG 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, Scope of Authorization.

B. Terumo BCT, Inc. and/or Marker Therapeutics AG may request changes to the authorized labeling and fact sheets. Such requests will be made in consultation with, and require concurrence of, DHT3A/OHT3/OPEQ/CDRH.

C. Terumo BCT, Inc. and/or Marker Therapeutics AG may request changes to the components and materials. Such requests will be made in consultation with, and require concurrence of, DHT3A/OHT3/OPEQ/CDRH.

D. Terumo BCT, Inc. and Marker Therapeutic AG will have a process in place to collect information on the performance of your products and for reporting adverse events of which they become aware to FDA under 21 CFR Part 803. Adverse events of which the manufacturer becomes aware will be reported to FDA.

E. Terumo BCT, Inc. and Marker Therapeutics AG 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.

F. Terumo BCT, Inc. and Marker Therapeutics AG will notify FDA of any authorized distributor(s) of the product, including the name, address, and phone number of any authorized distributor(s), and provide authorized distributor(s) with a copy of this EUA.

Terumo BCT, Inc., Marker Therapeutics AG, and Authorized Distributor(s)[5]

G. Terumo BCT, Inc., Marker Therapeutics AG, and authorized distributor(s) will make the Spectra Optia Apheresis System and the Depuro D2000 Adsorption Cartridge available with the authorized labeling and fact sheets, described in the Scope of Authorization (Section II) of this letter.

H. Terumo BCT, Inc., Marker Therapeutics AG, and authorized distributor(s) will make available on their website(s) the Fact Sheet for Healthcare Providers and the Fact Sheet for Patients.

I. All descriptive printed matter relating to the use of the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge shall be consistent with the authorized labeling and

[5] "Authorized Distributor(s)" are identified by the sponsor in EUA requests as an entity allowed to distribute the product.

fact sheets. No descriptive printed matter relating to the use of the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge may represent or suggest that this product is safe or effective for the prevention or treatment of COVID-19.

J. Terumo BCT, Inc., Marker Therapeutics AG, and authorized distributor(s) will 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.

K. Through a process of inventory control, Terumo BCT, Inc., Marker Therapeutics AG, and authorized distributor(s) will maintain records of the healthcare settings to which they distribute the Spectra Optia Apheresis System and Depuro D2000 Adsorption Cartridge and number of products they distribute.

L. Terumo BCT, Inc., Marker Therapeutics AG, 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.

Conditions Related to Advertising and Promotion

M. All advertising and promotional descriptive printed matter relating to the use of Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge 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.

N. No advertising or promotional descriptive printed matter relating to the use of the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge may represent or suggest that such products are safe or effective for the prevention or treatment of patients who have COVID-19.

O. All advertising and promotional descriptive printed matter relating to the use of the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge clearly and conspicuously shall state that:

- the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge have neither been cleared or approved for the indication to treat patients with COVID-19 infection;

- the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge have been authorized by FDA under an EUA;

- the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge are authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

V. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge 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,

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RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures