April 10, 2020

Mr. Vincent Capponi
CytoSorbents, Inc.
7 Deer Park Drive Suite K
Monmouth Junction, NJ 08852

Dear Mr. Capponi:

This letter is in response to CytoSorbents, Inc.'s request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of the CytoSorb device[1] (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]

There are no FDA approved, licensed, or cleared device treatments for COVID-19. Based on bench performance testing and reported clinical experience, FDA has concluded that the CytoSorb device may be effective at treating certain patients with confirmed COVID-19 by removing various pro-inflammatory cytokines from their blood. 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.

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[1] The CytoSorb device, CytoSorb 300 mL, was granted the European CE Mark in 2011 for cytokine adsorption, with subsequent expansions approved for bilirubin and myoglobin adsorption, as well as $P2Y_{12}$ Inhibitor-Ticagrelor removal.

[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).

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 CytoSorb device 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 CytoSorb device 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 CytoSorb device 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 CytoSorb device, when used to treat such patients, outweigh the known and potential risks of the CytoSorb device; and

3. There is no adequate, approved, and available alternative to the emergency use of the CytoSorb device 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 CytoSorb device 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 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 $\geq$ 30/min,
    3) blood oxygen saturation $\leq$ 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,

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

2) septic shock, and/or
3) multiple organ dysfunction or failure.

**Authorized Product Details**

1. The CytoSorb device is comprised of the following components and materials:

| Component Description | Materials of Construction |
|---|---|
| Cylinder (Device Body) | Polycarbonate |
| Screen Assembly (Over-Molded) | Ring: Polypropylene<br>Screen: Sefar Medifab |
| Silicone O-ring | Silicone |
| End Cap | Polycarbonate |
| Polymer (Adsorbent) | Crosslinked Divinylbenzene/polyvinylpyrrolidone |
| Port plug | Polypropylene |

2. The CytoSorb device mechanism of function is as follows:

   The CytoSorb device is designed for use in extracorporeal circuits to adsorb endogenous pathogenic mediators (e.g., inflammatory cytokines) that may be injurious under specific circumstances.

   The device can be incorporated into a number of extracorporeal circuits. In the ICU setting, the CytoSorb device is typically integrated into a continuous renal replacement therapy (CRRT) machine for hemoperfusion alone (i.e., with no dialysis filter) or, more commonly, in series with a dialysis filter as CRRT is also often being performed at the same time. In high flow applications, such as extracorporeal membrane oxygenation (ECMO), the CytoSorb device is integrated into the circuit off the main flow via a parallel (shunt) circuit, taking only a fraction of the typical 2-3 L/min/m2 of flow.

   The CytoSorb device is designed as a platform technology based on uniformly sized sorbent beads. Each bead is roughly the size of a grain of salt (~500 microns). The sorbent beads are composed of a divinylbenzene polymer with a polyvinyl pyrrolidone coating, where each bead has hundreds of thousands of tightly controlled pores and channels that are generated via suspension polymerization. At either end of the cylinder, a fine mesh screen (200 microns) is placed to retain the polymer beads within the device. These pores and channels, in turn, enable the porous polymer beads to remove molecules ranging in size from low molecular weight small molecules (< 900 Daltons) to molecules approximately 60-kiloDaltons (kDa) in size from blood, based on pore capture (size) and surface adsorption. The beads possess increased adsorption capacity due to the surface

area (46,000 $m^2$ per ~300 ml cartridge) from the collective surface area from the pores and channels within each bead.

Proteins and other hydrophobic molecules less than approximately 60 kDa enter the pores and adsorb onto the surface of the hydrophobic CytoSorb device polymer, through a combination of non-polar interactions, hydrogen bonding, and van der Waals forces.

The pore structure limits the adsorption of molecules greater than 60 kDa, such as albumin (65 kDa) and excludes the uptake of larger substances, such as immunoglobulins (>150 kDa).

Adsorption is concentration dependent, with higher efficiencies at elevated concentrations and lower efficiencies at reduced concentrations. The reduced efficiencies at lower concentrations aid in minimizing the risk of overtreatment.

3. The following device settings have been validated for operation of the CytoSorb device:

| Flow Resistance (HCT 32 ± 3% @ 37 ± 1° C) | |
|---|---|
| Qb ≤ 700 mL/min: | 140 mmHg |
| Qb ≤ 500 mL/min: | 90 mmHg |
| Qb ≤ 200 mL/min: | 30mmHg |
| Blood Priming Volume | 150 mL |
| Maximum Blood Flow Rate: | 700 mL/min |
| Minimum Blood Flow Rate: | 100 mL/min |
| Recommended Blood Flow Rate | 150-500 mL/min |
| Maximum Pressure Limit: | 760 mmHg |
| Storage Fluid: | Isotonic Saline |
| Priming Fluid: | Isotonic Saline |

Additional treatment information has been provided in the CytoSorb Instructions for Use, which is authorized under this EUA.

The CytoSorb device, when labeled consistently with the labeling authorized by FDA, entitled "CytoSorb 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 CytoSorb device is 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 of the CytoSorb device for COVID-19

- Fact Sheet for Patients: Emergency Use of the CytoSorb device 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 CytoSorb device, 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, 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 CytoSorb device 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 CytoSorb device, 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 the authorized product 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 CytoSorb device, 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:

**CytoSorbents, Inc.**

A. CytoSorbents, Inc. 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. CytoSorbents, Inc. may request changes to the authorized labeling and fact sheets. Such requests will be made in consultation with, and require concurrence of, DHT3/OHT3/OPEQ/CDRH.

C. CytoSorbents, Inc. may request changes to the components and materials. Such requests will be made in consultation with, and require concurrence of, DHT3/OHT3/OPEQ/CDRH.

D. CytoSorbents, Inc. may request changes to the Scope of Authorization (Section II in this letter) of your product. Such requests will be made in consultation with DHT3/OHT3/OPEQ/CDRH, and require concurrence of, Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC) and DHT3/OHT3/OPEQ/CDRH.

E. CytoSorbents, Inc. may request the addition of other instruments and associated software for use with your product. Such requests will be made in consultation with, and require concurrence of, DHT3/OHT3/OPEQ/CDRH.

F. CytoSorbents, Inc. may request the addition of other extraction methods for use with your product. Such requests will be made in consultation with, and require concurrence of, DHT3/OHT3/OPEQ/CDRH.

G. CytoSorbents, Inc. will have a process in place to collect information on the performance of their products and for reporting adverse events of which they become aware to FDA under 21 CFR Part 803. Adverse events of which the CytoSorbents, Inc. becomes aware will be reported to FDA.

H. CytoSorbents, Inc. is 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.

I. CytoSorbents, Inc. 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.

**CytoSorbents, Inc. and Authorized Distributor(s)[5]**

J. CytoSorbents, Inc. and authorized distributor(s) will make CytoSorb devices available with the authorized labeling and fact sheets, described in the Scope of Authorization (Section II) of this letter.

K. CytoSorbents, Inc. and authorized distributor(s) will make available on their website(s) the Fact Sheet for Healthcare Providers and the Fact Sheet for Patients.

L. All descriptive printed matter relating to the use of the CytoSorb shall be consistent with the authorized labeling and fact sheets. No descriptive printed matter relating to the use of the CytoSorb may represent or suggest that this product is safe or effective for the prevention or treatment of COVID-19.

M. CytoSorbents, Inc. 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.

N. Through a process of inventory control, CytoSorbents, Inc. and authorized distributor(s) will maintain records of the healthcare settings to which they distribute the CytoSorb and number of CytoSorb they distribute.

O. CytoSorbents, Inc. 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**

P. All advertising and promotional descriptive printed matter relating to the use of the CytoSorb device 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 advertising or promotional descriptive printed matter relating to the use of the CytoSorb device may represent or suggest that such products are safe or effective for the prevention or treatment of COVID-19.

R. All advertising and promotional descriptive printed matter relating to the use of the CytoSorb device clearly and conspicuously shall state that:

- the CytoSorb device has neither been cleared or approved for the indication to treat patients with COVID-19 infection;
- the CytoSorb device has been authorized by FDA under an EUA;

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

- the CytoSorb device is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of the CytoSorb device 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 CytoSorb device 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